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Review Article

Clinical Pharmacology of Trimethoprim-Sulfamethoxazole in Infants and Children

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Abstract

Trimethoprim-sulfamethoxazole, also called co-trimoxazole, is available as a single-entity preparation, and the introduction in clinic of trimethoprim-sulfamethoxazole is an important advance in the treatment of bacterial infections. Trimethoprim inhibits bacterial reductase an enzyme downstream from the one that sulphonamides inhibit in the same biosynthetic sequence. This formulation consists in a dose of sulfamethoxazole 20-fold greater than that of trimethoprim, 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* species, even among methicillin-resistant isolates, viridians group of *streptococci, Escherichia coli, Proteus mirabilis, Klebsiella* and *Enterobacter* species, *Salmonella, Pseudomonas pseudomallei, Serratia* species, *Pasteurella haemolytica, Yersinia* species, and *Nocardia asteroides*. The oral dose of co-trimoxazole is 120 mg twice-daily in infants. In children aged up to 5 years, 6 to 11 years, and 12 to 17 years, the oral dose is 240, 480, and 960 mg, respectively, twice-daily. Trimethoprim-sulfamethoxazole is efficacy and safe in infants and children but it 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 hours, respectively. Co-trimoxazole inhibits CYP2C8 and CYP2C9. Prophylaxis and treatment with trimethoprim-sulfamethoxazole have been performed in infants and children and this drug-combination successfully cured the meningitis caused by *Listeria meningitides, Listeria monocytogenes, Nocardia meningitis, Elizabethkingia meningoseptica*, and *Staphylococcus aureus*. The aim of this study is to describe the dosing, efficacy and safety, adverse-effects, pharmacokinetics, interaction with drugs, prophylaxis, treatment, meningitis, in infants and children.

Keywords: Trimethoprim-sulfamethoxazole; Dosing; Pharmacokinetics; Prophylaxis; Treatment; Meningitis

Introduction

Trimethoprim-sulfamethoxazole

Trimethoprim inhibits bacterial dihydrofolate reductase, an enzyme downstream from 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. In much of the world, the combination of trimethoprim with sulfamethoxazole is known as co-trimoxazole, and the combination of sulfamethoxazole with trimethoprim is available as single-entity preparation [1].

Mechanism of action of trimethoprim-sulfamethoxazole

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). Selective toxicity for microorganisms is reached in two ways. 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 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:trimethoprin. 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* (Figure 1) [1].

Literature search

The literature search was performed electronically using

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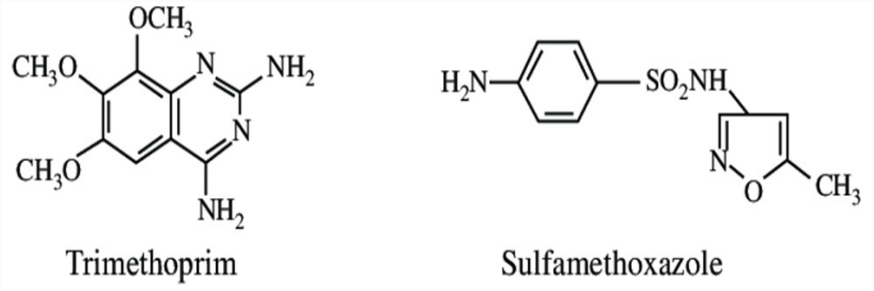

Figure 1: Molecular structure of trimethoprim and sulfamethoxazole.
Molecular weight of trimethoprim=290.32 grams/mole and molecular weight of sulfamethoxazole=253.28 grams/mole.

PubMed database as search engine. The following key words were used: "co-trimoxazole dosing infants, children", "trimethoprim-sulfamethoxazole efficacy and safety infants, children", "trimethoprim-sulfamethoxazole adverse-effects infants, children", "trimethoprim and sulfamethoxazole pharmacokinetics", "trimethoprim and sulfamethoxazole metabolism", "trimethoprim-sulfamethoxazole drug interactions", "trimethoprim-sulfamethoxazole prophylaxis infants, children", "trimethoprim-sulfamethoxazole treatment infants, children", and "trimethoprim-sulfamethoxazole meningitis infants, children". In addition, the books: The Pharmacological Basis of Therapeutics [1] and the Births National Formulary for Children [2] were consulted.

Results

Oral treatment of susceptible infections with co-trimoxazole to infants [2].

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 to children [2].

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.

Intravenous treatment of susceptible infections with co-trimoxazole to children [2].

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

Oral treatment of *Pneumocystis Jirovecil* (*Pneumocystis carinii*) (undertaken where facilities for appropriate monitoring are available - consult microbiologist and product literature).

Children. Give: 120 mg/kg daily in 2 to 4 divided doses for 14 to 21 days. Oral route preferable for children.

Oral prophylaxis of *Pneumocystis Jiroveci* (*Pneumocystis carinii*) infections.

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) dose regimen may vary, consult local guidelines.

Efficacy and safety of sulfisoxazole-trimethoprim in infants and children.

Infants and children, aged 6 months to 13 years, with uncomplicated urinary-tract infections were treated with trimethoprim/sulfamethoxazole at a dose of 8/40 mg/kg twice-daily. No treatment failures were observed, mild adverse-effects appeared in only 16% of subjects and this treatment was efficacy and safe in infants and children [3]. Co-trimoxazole is safe and efficacious for the treatment of *Plasmodium falciparum* malaria in children irrespective of HIV-status and antifolate resistant profiles. Co-trimoxazole is also efficacy and safe in the prophylaxis of malaria caused by *Plasmodium falciparum* in children in specific HIV-negative children [4]. Co-trimoxazole was administered to 20 children, aged 9 months to 17 years, at a dose of 16.4 mg/kg daily for 26 to 59 days. Children were suffering from osteomyelitis, only 8 children (40.0%) had mild adverse-effects, and co-trimoxazole was useful and well tolerated [5]. Twenty children suffering from pneumonitis caused by *Pneumocystis carinii* were treated with 20 mg/kg of trimethoprim and 100 mg/kg sulfamethoxazole daily. The treatment was efficacy and safe with a favourable benefit-risk ratio for all children [6]. Children (N=334) had no-obstructed urinary-tract infection, 167 children (50.0%) had vesico-ureteric reflux and 27 children (8.1%) had renal scarring. All these children were treated with co-trimoxazole and neither an increase in recurrent infections were observed nor a significant modification of therapy occurred and co-trimoxazole was effective and safe prophylactic agent [7].

Adverse-effects caused by trimethoprim-sulfamethazine in children

In 234 children treated for melioidosis there are high rates of adverse-effects caused by oral trimethoprim-sulfamethoxazole which was administered for 3 to 6 months and frequently necessitating a change of treatment or a reduction in the dose. Of these, 16 children (6.8%) died during treatment and 6 children (2.6%) did not complete the therapy. Given the adverse-effects the treatment was interrupted [8]. Trimethoprim-sulfamethoxazole was administered to two subjects and induced aseptic meningitis [9]. Trimethoprim-sulfamethoxazole was administered to 99 children. Initially, trimethoprim-sulfamethoxazole usage was strongly associated with appearance on integron-positive multidrug-resistant Enterobacteriaceae in the intestinal flora. After prolonged exposure to this drug combination, however, this population of Enterobacteriaceae was substituted by a population with non-integron-associated resistance-mechanisms, and after trimethoprim-sulfamethoxazole was discontinued, susceptibility-rates returned to baseline levels [10]. Treatment with

trimethoprim-sulfamethoxazole to children causes cutaneous (1.4 to 7.4%), haematological toxicity (0 to 72%) and hepatotoxicity (5%) adverse-effects but serious adverse-effects are extremely rare and most are reversible by discontinuance of therapy. These adverse-effects appear less frequently in children than in adults [11]. The development of haematological abnormalities was evaluated in 50 children. Neutropenia occurred in 17 children (34.0%) and thrombocytopenia developed in 6 children (12.0%). Neutropenia lasted for 9 days and thrombocytopenia was noted for 13 day, thus these adverse-effects disappeared after the cessation of treatment [12].

Pharmacokinetics of trimethoprim and sulfamethoxazole in infants and children

Autmizguine et al. [13] studied the pharmacokinetics of trimethoprim and sulfamethoxazole in 153 infants and children with median and 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%) were white, 29 (19%) were block 3 (2%) were of unknown origin, and 12 (8%) of other origins. The subject ethnicity was Hispanic 26 (17%), not Hispanic 123 (80%), and 4 (3%) of unknown ethnicity. The median trimethoprim and sulfamethoxazoledoses were: 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 were: 4.6 mg (range, 2.5 to 60.2) and 23.0 (range, 2.5 to 120). The median dose interval was 12 hours (range, 6 to 48). Seventy-eight subjects (51%) received an oral suspension of trimethoprim/sulfamethoxazole at 8/40 mg/ml) at the time of the first recorded dose, while the remaining subjects received trimethoprim/sulfamethoxazole tablets at 80/400 mg or 160/800 mg. Dosing was *via* the oral route in 125 subjects (82%), *via* a gastrostomy tube 17 subjects (11%), and by other routes in 11 subjects (7%) (Tables 1-4).

Thompson et al. [14] explored the pharmacokinetics of trimethoprim and sulfamethoxazole in 54 infants and children. Twelve infants had a median postmenstrual, postnatal ages and body-weight of 63.4 weeks (range, 47.1 to 91.3), 0.45 years (range, 0.18 to 0.98), and 5.8 kg (range, 3.98 to 9.5), 10 children had a median postmenstrual, postnatal ages and body-weight of 111 weeks (range, 94.6 to 139), 1.36 years (range, 1.05 to 1.91), and 9.95 kg (range, 6.94 to 11.6), 9 children had a median postmenstrual, postnatal ages and body-weight of 261 weeks (168 to 348), 4.23 years (range, 2.45 to 5.9), and 16.6 kg (range, 10.5 to 22.4), 5 children had a median postmenstrual, postnatal ages and body-weight of 450 weeks (range, 407 to 517), 7.86 years (range, 7.04 to 8.14), and 22.5 kg (range, 17.4 to 32.3), and 18 children had a median postmenstrual, postnatal ages and body-weight of 876 weeks (range, 678 to 1,012), 16.0 years (range, 12.2 to 18.6), and 51.8 kg (range, 33.2 to 69.0). The exposures for trimethoprim and sulfamethoxazole were determined by the AUC at steady-state, and this was calculated as a product of dose-interval and the mean steady-state concentration of both drugs after recommended dose for treating methicillin resistant *Staphylococcus aureus* (oral 156 mg of trimethoprim/800 mg of sulfamethoxazole twice-daily). For trimethoprim, the reference adult exposure is AUCss >20.6 μg*h/ml. The safety margins of trimethoprim (peak plasma concentration=114 μg/ml, AUCss=142 μg*h/ml) and for sulfamethoxazole (peak plasma concentration=372 μg/ml and AUCss=4,119 μg*h/ml) (Tables 5 and 6).

Inhibition of cytochromes P-450 (CYPs) by trimethoprim and sulfamethoxazole

It was evaluated the inhibitory effects of trimethoprim-sulfamethoxazole on cytochrome P450 isoforms, selective marker reactions for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 were examined in human liver microsomes and recombinant CYP2C8 and CYP2C9. The *in-vivo* drug interactions of trimethoprim and sulfamethoxazole were predicted *in-vitro* using [I]/[I] + Ki values. With concentrations ranging from 5 μM to 100 μM, trimethoprim exhibited 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 μM 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 (271 μM) and 456 μM, respectively. With concentrations higher than 100 μM trimethoprim and 500 μM sulfamethoxazole, both drugs lost their selectivity for the P450 isoforms. Based on estimated total hepatic concentrations (or free plasma concentrations) of the drugs and the scaling model, one would expect *in-vivo* in humans 80% (26%) and 13% (24%) inhibition of the metabolic clearance of CYP2C8 and CYP2C9 substrates by trimethoprim and sulfamethoxazole, respectively. In conclusion, trimethoprim and sulfamethoxazole can be used as selective inhibitors of CYP2C8 and CYP2C9 in *in-vitro* studies. In humans, trimethoprim and sulfamethoxazole may inhibit the activities of CYP2C8 and CYP2C9, respectively [15].

Interaction of trimethoprim-sulfamethoxazole with drugs

Trimethoprim-sulfamethoxazole interacts with warfarin and induces high risk for serious bleeding events [16]. Relevant publications that directly or indirectly addressed the vitamin K trimethoprim-sulfamethoxazole interaction have been reviewed. The mechanism of the vitamin K trimethoprim-sulfamethoxazole interaction causes increased risk of bleeding. Concurrent use of vitamin K and trimethoprim-sulfamethoxazole should be avoided when possible. When vitamin K and trimethoprim-sulfamethoxazole are co-prescribed, vitamin K dose should be reduced [17]. Methotrexate and trimethoprim-sulfamethoxazole combination causes extremely serious and life-threatening effects and this drug association should be avoided. Practical recommendations regarding methotrexate use can be established to prevent harm effects caused by this drug interaction [18]. 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 with angiotensin-converting enzyme inhibitors, potassium supplements, and potassium-sparing diuretics. In addition, hyponatremia has been associated with thiazide diuretics and trimethoprim therapy. Trimethoprim and sulfamethoxazole are selective inhibitors of CYP2C8 and CYP2C9, respectively. Inhibition of these CYP isoenzymes serves as a potential mechanism of drug-drug interactions between trimethoprim-sulfamethoxazole and glipizide, phenytoin, reparglinide, rosiglitazone, and tolbutamide. Trimethoprim-sulfamethoxazole may accelerate the metabolism of cyclosporine, resulting in lower serum cyclosporine concentrations. Additive inhibition of dihydrofolate reductase to azathioprine, methotrexate, or pyrimethamine contributes, in part, to the increased risk for myelotoxicity, pancytopenia, or megaloblastic anaemia when these agents are combined with trimethoprim or sulfamethoxazole [19].

Table 1: Pharmacokinetic parameters of trimethoprim obtained from the final model, by Autmizguine et al. [13].

	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	5.5	8.8	9.9	11
DV/F_{70kg} (L)	148	6.8	129	148	173
TM_{50} (years)	0.24	24.8	0.14	0.24	0.4
Hill coefficient in the E_{max} maturation function 1 (fixed)					
Exponent of SCR effect on TBC/F	0.4	20.4	0.26	0.41	0.57
IIV (TBC/F) (%CV)	33.8	36.8	10	31.6	44.7
IIV (DV/F) (%CV)	20.6	89.2	4.7	22.3	50.1
Proportional error (%)	51.1	14.4	42.3	50	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 to70 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 in Total Body Clearance; IIV (DV/F): Interindividual Variability in the Distribution Volume; CV: Coefficient of Variation; F: Bioavailability.

This table shows that trimethoprim is rapidly absorbed following oral administration, trimethoprim is distributed in a volume larger the water volume, and there is a remarkable interindividual variability in the pharmacokinetic parameters.

Table 2: Trimethoprim individual empirical Bayesian post hoc parameter estimates stratified by age. Figures are the median and range, by Autmizguine et al. [13].

	Median (range) value for the following age groups (years)			
Parameter	**0 to <2 years (N=46)**	**2 to <6 years (N=25)**	**6 to <21 years (N=82)**	**Total (N=153)**
TBC/F (L/h/kg)	0.25 (0.05 - 0.44)	0.23 (0.14 - 0.43)	0.14 (0.04 - 0.31)	0.16 (0.0 - 0.44)
TBC/F (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/F (L/kg)	2.1 (1.8 - 2.5)	2.1 (1.8 - 2.4)	2.1 (1.4 - 2.4)	2.1 (14 - 2.5)
DV/F (L/70 kg)	149 (125 - 175)	149 (127 - 171)	147 (96 - 168)	148 (96.2 - 175)
*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. *Elimination half-life.

This table shows that the total body clearance, expressed as L/h/kg, is higher in younger subjects, the distribution volume is independent by the subject age, the elimination half-life increases with the subject age, and there is a remarkable variability in the pharmacokinetic parameters.

Table 3: Pharmacokinetic parameters of sulfamethoxazole obtained from the final model, by Autmizguine et al. [13].

	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	0.6	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	2.3	59.6	0.3	2.3	11.4
Exponent for ALB effect on TBC/F	-0.77	34	-1.5	-0.76	-0.20
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/F70kg: Total Body Clearance Scaled to a 70 kg adult; DV/F70kg: Distribution Volume Scaled to 70 kg adult; TM50: 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 the 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.

This table shows that the absorption rate constant, total body clearance, distribution volume, and the elimination half-life are smaller than those of trimethoprim and that there is a remarkable variability in the pharmacokinetic parameters.

Prophylaxis with trimethoprim-sulfamethoxazole in infants and children

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 the placebo. Based on an analysis of data from a large clinical trial of trimethoprim-sulfamethoxazole prophylaxis, there were no evidence that prolonged exposure to this antibiotic has a concurrent effect on weight gain or the prevalence of overweight or obesity in healthy infants and children [20]. *Pneumocystis jirovecii* infection causes fulminant interstitial pneumonia (*Pneumocystis pneumonia*) in patients with rheumatoid arthritis. 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 [21]. One-hundred-eight-five infants and children, aged 6 weeks to 9 months, were randomly assigned to discontinue co-trimoxazole or to perform prophylaxis with this drug for 2 years. Prophylaxis with co-trimoxazole resulted to be effective in preventing infections [22]. Long-term prophylaxis with low-dose of trimethoprim-sulfamethoxazole was associated with a decreased number of urinary-tract infections in predisposed children. The prophylaxis appeared to be consistent but modest differences were observed across children age subgroups [23]. Trimethoprim-sulfamethoxazole has been used for the prophylaxis of urinary-tract infection in infants and children. These subjects with risk factors, long-term antibiotic prophylaxis should be considered, at least there is evidence that these subjects are not endangered by

Table 4: Simulated trimethoprim exposure at steady stale. Figures are the median and (range), by Autmizguine et al. [13].

		$AUC_{0-\Gamma,ss}$ (mg*h/L) data are the median and (2.5th to 97.5th percentile)					
		Oral dosing every 12 hours		Oral dosing every 8 hours		Oral dosing every 6 hours	
Age group (years)	No. of subjects	8 mg/kg daily[a]	12 mg/kg daily[b]	15 mg/kg daily[c]	20 mg/kg daily[d]	15 mg/kg daily[e]	20 mg/kg daily[f]
0 to <2	500	19.2 (9.2 - 59.1)	28.7 (13.8 - 88.7)	23.9 (11.5 - 73.9)	32.1 (15.4 - 99.0)	17.9 (58.6 - 55.4)	23.9 (11.5 - 73.9)
2 to <6	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	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 - 47.8)	30.7 (15.7 - 63.7)
18 to 21	500	19.2 (10.2 - 39.5)	39.1 (20.3 - 79.0	42.8 (22.2 - 86.4)	57.3 (29.7 - 116)	32.1 (16.6 - 64.8)	42.8 (22.2 - 86.4)

$AUC_{0-\Gamma,ss}$: AUC at steady-state from 0 to Γ (where Γ denotes the dosing interval); aMaximum daily dose 320 mg (1 double-strength tablet every 12 hours) achieved at a body-weight of 40 mg. bMaximum daily dose 640 mg (2 double-strength tablets every 12 hours) achieved at a body-weight of 53 kg. cMaxumum daily dose 1,200 mg (2 double-strength tables + 1 single-strength tablet every 8 hours) achieved at a body-weight of 60 kg. dMaximum daily dose 1,440 mg (3 double-strength tablets every 8 hours) achieved at a body-weight of 85 kg. eMaximum daily dose 1,200 mg (2 double-strength tablets every 6 hours) achieved at a body-weight of 85 kg. fMaximum daily dose 1,600 mg (2 double-strength tablets + 1 single-strength tablets every 6 hours) achieved at a body-weight of 80 mg.

This table shows that the various AUC estimates of trimethoprim increases with the subject age and thus with the trimethoprim dose.

Table 5: Percentage of virtual subjects achieving trimethoprim pharmacokinetic targets (AUSss >20.6 μg*h/ml) PD targets (trimethoprim concentration in skin >2 μg/ml), and exceeding safety margins (AUCss >142 μg*h/ml and peak concentration >13.6 μg/ml) with age-based trimethoprim-sulfamethoxazole dosage-regimens.

Age group (postnatal age)	Trimethoprim dose (mg/kg) twice-daily	%Subjects with AUCss >20.6 μg*h/ml	%Subjects with trimethoprim in skin > 2 μg/ml for half of dosing-interval	%Subjects with AUCss >142 μg*h/ml	%Subjects with peak concentration >13.6 μg/ml
>2 months to 20 weeks	6	91	90	0	0
<5 months to 1 year	6	84	84	0	0
>1 to 6 years	6	86	87	0	0
>6 to 12 years	6	93	64	0	0
>12 to 18 years	4	91	92	0	0

This table shows that the target values of AUCss >20.6 μg*h/ml of trimethoprim and trimethoprim peak concentration >2 μg/ml were achieved in all subjects and excessive values of AUCss >142 μg*h/m excessive skin concentration of trimethoprim >13.6 μg/ml were not achieved in any subject.

Table 6: Percentage of virtual patients achieving sulfamethoxazole pharmacokinetic targets (AUCss >816 μg*h/ml), PD targets (sulfamethoxazole concentration in skin >9.5 μg/ml), and exceeding safety of margins (AUCss >4,119 μg*h/ml and peak concentration >372 μg/ml) with age-based trimethoprim-sulfamethoxazole dosing-regimen.

Age group (postnatal age)	Sulfamethoxazole dose (mg/kg) twice-daily	%Subjects with AUCss > 816 μg*h/ml	%Subjects with sulfamethoxazole in skin > 9.6 μg/ml for half of dosing-interval	%Subjects with AUCss > 4,116 μg*h/ml	%Subjects with peak concentration >372 μg/ml
>2 months to 20 weeks	30	74	100	0	0
>5 months to 1 year	30	63	99	0	0
>1 to 6 years	30	78	100	1	1
>6 to 12 years	30	92	99	0	0
>12 to 18 years	20	85	98	0	0

This table shows that the majority of subjects achieved the target value of AUCss >816 μg*h/ml and the skin concentration >9.6 μg/ml of sulfamethoxazole and only 1 subject achieved excessive AUCss >4,116 μg*h/ml and excessive peak concentration >372 μg/ml of sulfamethoxazole.

avoiding it [24]. Children affected by falciparum malaria received prophylaxis with trimethoprim-sulfamethoxazole. In this setting of low antifolate resistance, trimethoprim-sulfamethoxazole was highly effective in preventing falciparum malaria infection and treatment did not appear to select sulfadoxine-pyrimethamine resistant parasites [25].

Treatment with trimethoprim-sulfamethoxazole in infants and children

Trimethoprim sulfamethoxazole should be considered in the treatment of neonatal *Flavobacterium meningosepticum* sepsis in view of its activity against this organism, good penetration of the blood brain barrier, and the absence of serious side effects in infants [26]. Trimethoprim-sulfamethoxazole provides therapeutic activity against *Pneumocystis carinii* and trimethoprim-sulfamethoxazole is also used for the treatment of pulmonary and disseminated nocardiosis and some forms of Wegener's granulomatosis in children [27]. Trimethoprim-sulfamethoxazole was administered to 37 infants and children, aged 6 months to 13 years, at doses of 8 and 10 mg/kg, respectively, daily and Escherichia coli was the most common isolate. Eight-five percent of this organism was susceptible; the treatment lasted for 7 to 10 days, and successfully cured the infection caused by this pathogen [28]. Intravenous trimethoprim-sulfamethoxazole was administered at doses of 10 and 50 mg/kg, respectively, 4 times-daily, to 18 infants and children, aged 3 weeks to 13 years, suffering from serious infections caused by *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes,* or *Acinetobacter anitratus*. This treatment successfully cured the infections and the adverse-effects were frequent but reversible [29]. Trimethoprim-sulfamethoxazole was administered orally for 3 to 4 days to children, aged 10 months to 15 years, suffering from salmonellosis and this treatment cured the infection causes by *Salmonella gastroenteritis* [30].

Penetration of trimethoprim-sulfamethoxazole into the Cerebrospinal Fluid (CSF) and treatment of meningitis in infants and children

Trimethoprim-sulfamethoxazole was administered to a patient with Listeria meningitides and the ratio into the CSF was 1 to 8 [31]. A single intravenous dose 5 mg of trimethoprim and 25 mg of sulfamethoxazole was administered to patients. The peak of trimethoprim and sulfamethoxazole occurred 60 and 480 min, respectively, after the infusion. In the post-infusion phase, the concentration of trimethoprim was 0.23 and 0.53 μg/ml in the CSF and serum, respectively, and that of sulfamethoxazole was 0.20 and 0.36 μg/ml, respectively [32].Trimethoprim was administered to patients orally and intravenously and has property of excellent penetration into the CSF even when the meninges are not inflamed; oral or intravenous dosing achieved high concentration in the CSF [33]. An infant aged 7 month had meningitis caused by Listeria monocytogenes which did not respond to ampicillin and an aminoglycoside whereas it was successfully cured with trimethoprim-sulfamethoxazole [34]. An extremely premature infant had the meningitis caused by Elizabethkingia meningoseptica and was successfully cured by trimethoprim-sulfamethoxazole [35]. A patient with Nocardia meningitis was treated with trimethoprim-sulfamethoxazole and the infection disappeared [36]. Two patients had meningitis caused *Staphylococcus aureus* and other two patient had meningitis due to Listeria monocytogenes and meningitis was cured with trimethoprim-sulfamethoxazole in all patients [37].

Discussion

Trimethoprim inhibits bacterial reductase an enzyme downstream from the one that sulphonamides inhibit in the same biosynthetic sequence. The combination of trimethoprim with sulfamethoxazole was an important advance in the development of clinical effective and synergistic antimicrobial agents. Trimethoprim-sulfamethoxazole is available as single-entity preparation and is also called 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*, *S. aureus* and *Staphylococcus epidermis* remain susceptible. *Streptococcus pyogenes,* the viridians group of *streptococci, Escherichia coli, Proteus mirabilis, Klebsiella* species, *Enterobacter* species, *Salmonella, Pseudomonas pseudomallei, Serratia,* and *Alcaligenes* species, *Brucella abortus, Pasteurella haemolytica, Yersinia pseudotuberculosis, Yersinia enterocolitica,* and *Nocardia asteroidesare* susceptible [1]. The oral dose of co-trimoxazole is 120 mg twice-daily in infants and 240, 480, and 960 mg to children aged up to 5 years, 6 to 11 years, and 12 to 17 years, respectively, twice-daily [2]. Trimethoprim-sulfamethoxazole is efficacy and safe in infants and children [3-7], but may induce some adverse-effects in children [8-12] and the adverse-effects may be serious, may cause death and may require the interruption of treatment [8]. Other adverse-effects are: the induction of aseptic meningitis [9], modification of Enterobacteriaceae-sensitivity [10], hematologic and hepatic toxicity [11], and this drug-combination also induces haematological abnormalities [12] including neutropenia and thrombocytopenia [13]. Following oral administration both drugs are rapidly absorbed and the absorption rate constant is 1.27 and 0.58 for trimethoprim and sulfamethoxazole, respectively. In infants and children with a body-weight ranging from 2.4 kg to 148 kg the total body clearance was 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 trimethoprim elimination half-life ranges from 5.9 to 11.1 hours and increases with the child age [13]. Trimethoprim-sulfamethoxazole is a potent inhibitor of CYP2C8 and CYP2C9 [15]. Trimethoprim-sulfamethoxazole interacts with vitamin K [16] and increases the risk of bleeding [17], the association of methotrexate with trimethoprim-sulfamethoxazole causes life-threating adverse-effects [18]. Trimethoprim inhibits the renal tubular secretion and increase the plasma concentration of amantadine, dapsone, digoxin, dofetilide, lamivudine methotrexate, procainamide, and zidovudine [19]. Prophylaxis with trimethoprim-sulfamethoxazole has been studied in infants and children [20-25] and it has been found useful to prevent the infection caused by *Pneumocystis jirovecii* [21], prevents different infections [22], decreased the number of urinary-tract infections [23,24], and prevented falciparum malaria [25]. Treatment with trimethoprim-sulfamethoxazole has been assessed in infants and children [26-30] and has been found useful to cure *Flavobacterium meningosepticum* sepsis [26], pulmonary infection caused by *Pneumocystis carinii* [27], by *Escherichia coli* [28], by *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes* or *Acinetobacter anitratus* [29], and by *Salmonella gastroenteritis* [30]. Trimethoprim penetrates into the cerebrospinal fluid more rapidly than sulfamethoxazole [31] but this drug-combination cured the meningitis caused by *Listeria meningitides* [32], *Listeria monocytogenes* [34], *Elizabethkingia meningoseptica* [36], *Nocardia meningitis*, and *Staphylococcus aureus* [37].

In conclusion, trimethoprim-sulfamethoxazole, also known as co-trimoxazole, inhibits bacterial reductase an enzyme downstream from the one that sulphonamides inhibit in the same biosynthetic sequence. The dose of sulfamethoxazole is 20-fold higher than that of trimethoprim and trimethoprim-sulfamethoxazole is administered as a single-entity preparation. Each agent alone is bacteriostatic but this drug combination may be bactericidal. *Staphylococcus aureus* and *epidermis, Streptococcus pyogenes*, the viridians group of *streptococci, Escherichia coli, Proteus mirabilis, Klebsiella* and *Enterobacter* species, *Salmonella, Pseudomonas pseudomallei, Serratia and Alcaligenes* species, *Brucella abortus, Pasteurella haemolytica, Yersinia* species and *Nocardia asteroides* are inhibited by trimethoprim-sulfamethoxazole. Oral dose of co-trimoxazole is 120 mg in infants and 240, 480, and 960 mg in children aged up to 5 years, 5 to 11 years, and 12 to 17 years twice-daily, respectively. Both drugs are rapidly absorbed by the gastrointestinal-tract but the absorption rate constant is greater for trimethoprim than sulfamethoxazole. The total body clearance and the distribution volume are greater for trimethoprim than sulfamethoxazole. Trimethoprim-sulfamethoxazole inhibits CYP2C8 and CYP2C9 and interacts with many drugs. Prophylaxis with trimethoprim-sulfamethoxazole has been found useful to prevent various infections and co-trimoxazole has been used to treat various infections. Trimethoprim-sulfamethoxazole successfully cured

meningitis caused by different bacteria. The aim of this study is to review the clinical pharmacology of trimethoprim-sulfamethoxazole 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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