Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 4 Number 4 April 1998

Trimethoprim-sulfamethoxazole: A Review of Use in Children

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Trimethoprim-sulfamethoxazole, also known as co-trimoxazole or TMP-SMX, was introduced in 1968 as a broad-spectrum antimicrobial agent. Trimethoprim was specially developed as a potentiator of sulphonamide to act synergistically against bacteria and delay the development of bacterial resistance.[1,2] Clinically, TMP-SMX is useful for prophylaxis and treatment of infections of the genitourinary, respiratory, and gastrointestinal tracts.[1,3] The therapeutic effectiveness of TMP-SMX for many infections of the pediatric population has contributed to its widespread use in children.

Mechanism of Action

The two components of TMP-SMX are inhibitors of bacterial synthesis of the metabolically active form of folic acid, tetrahydrofolic acid. Sulfamethoxazole is a structural analogue of para-aminobenzoic acid and inhibits the synthesis of dihydrofolic acid, a precursor of tetrahydrofolic acid. Trimethoprim is a structural analogue of the pteridine portion of dihydrofolic acid and acts as a competitive inhibitor of dihydrofolate reductase, the final enzyme in the pathway to tetrahydrofolic acid. The drug combination blocks two consecutive steps in the bacterial biosynthesis of essential nucleic acids and proteins.[3-5] In vitro, bacterial resistance develops more slowly with the combined product than with either drug alone.

Current Indications

TMP-SMX is currently approved by the FDA for use in adults and children with urinary tract infections (UTIs) due to susceptible strains of *E. coli*, Klebsiella and Enterobacter species, *M. morganii*, *P. mirabilis*, and *P. vulgaris*. It is also indicated in the treatment of Shigellosis enteritis caused by susceptible strains of *S. flexneri* and *S. sonnei* as well as the treatment of Travelers' diarrhea due to susceptible strains of *E. coli*.[4]

TMP-SMX is considered a first-line agent for treatment of acute otitis media in children due to susceptible strains of *Haemophilus influenzae* (including ampicillin-resistant strains) or *Streptococcus pneumoniae*.[6] Other indications include treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *H. influenzae* or *S. pneumoniae*.[4]

TMP-SMX remains the antimicrobial of choice for treatment of *Pneumocystis carinii* pneumonia (PCP).[5] It may be further used as prophylactic treatment against PCP in individuals who are immuno-compromised or considered at risk for PCP.[4] Parenteral therapy is indicated in severe infections or when oral therapy is not feasible.

While it is important to note that TMP-SMX covers a wide range of gram-positive and gram-negative bacteria, it is not effective in the treatment of infections due to *Pseudomonas aeruginosa*.[3,4]

Use in Children

TMP-SMX has been studied in a wide range of pediatric settings.[1] The FDA approved indications for the use of TMP-SMX in children include the treatment of urinary tract infections and acute otitis media due to susceptible organisms, as well as the treatment of *Shigellosis* enteritis and PCP.

TMP-SMX has also been administered as prophylaxis for many of these infections. Prevention of recurrent urinary tract infections with TMP-SMX has been documented in several studies. As an example, Sher[7] found that 5 children with recurrent UTIs who were given prophylactic therapy with TMP-SMX were free from recurrences during the five to seven month trial period. The comparison group of 5 children treated with other agents, including ampicillin and nitrofurantoin, experienced further UTIs.

Prevention of recurrent otitis media in children with frequently recurrent disease remains a controversial issue.[8,9] There are several studies that indicate antimicrobial prophylaxis may be

effective. Gaskins and colleagues[10] reported a significant decrease in acute otitis media in a sample of 21 children, aged 1 to 14 years, treated with standard doses of TMP-SMX compared to those receiving placebo over a 6 month period.

Prophylaxis of PCP in immunosuppressed children has also been well-studied.[11-15] Children with leukemia who are receiving chemotherapy have been found to have significantly fewer episodes of PCP, as well as other bacterial infections, when given TMP-SMX prophylaxis.[11,12] A reduction in febrile episodes during periods of neutropenia has also been documented during some of these trials.[12]

Similar benefit has been documented in children with immunodeficiency secondary to HIV infection.[13-16] The Center for Disease Control currently recommends that intermittent TMP-SMX be administered to children with AIDS who are considered to be at high risk for PCP infection.[13]

Pharmacokinetics

TMP-SMX is available in both oral and intravenous dosage forms. TMP-SMX is rapidly and completely absorbed following oral administration. Peak plasma levels occur 1 to 4 hours following oral administration and 1 to 1.5 hours after IV infusion. The 1:5 ratio of trimethoprim to sulfamethoxazole achieves an approximate 1:20 ratio of peak serum concentrations which is the optimal synergistic ratio of serum concentrations against most susceptible bacteria.[1,4,5]

Absorption, distribution, metabolism, and excretion of both antibiotics follow first-order kinetics. TMP-SMX is widely distributed throughout the body, including the CNS. Trimethoprim is 45% and sulfamethoxazole is 66% bound to plasma protein.[5] Fries and colleagues[17] have shown that the concentrations of trimethoprim and sulfamethoxazole in most tissues, including inflamed meninges, are approximately 30 to 50% and 20% respectively, of the concomitant plasma concentrations.

Both components cross the human placenta and are detectable in breast milk. Following oral administration, the half-lives of trimethoprim (8 to 11 hours) and sulfamethoxazole (10 to 12 hours) are similar in patients with normal renal function. In infants, the elimination half-life of both drugs may be longer than in adults. Both the parent compounds and the metabolites of the drug are excreted in the urine; however, only the parent compounds of both drugs are excreted in the bile.[3,4]

Drug Interactions

Trimethoprim may cause a decrease in the therapeutic effect of cyclosporine and an increased risk of nephrotoxicity.[4]

The serum concentrations of several drugs may be increased if given with trimethoprim. These drugs include: warfarin, dapsone, phenytoin, methotrexate, zidovudine, and sulfonylureas. Dosing of these drugs should be adjusted accordingly. Since severe cytopenias may occur with concomitant use of methotrexate, this combination should be avoided.[4]

Adverse Effects

Adverse effects are well documented for TMP-SMX. In two large-scale observational studies, Lawson[18] and Jick[19] reported the incidence of TMP-SMX-related adverse reactions in children and adults. The most frequent adverse effects caused by TMP-SMX were gastrointestinal upset (such as nausea, vomiting, and diarrhea) and skin rashes, occurring in 3 to 4% of patients. Approximately 1-4% of children who received TMP-SMX developed a mild toxic erythema.

Serious adverse reactions associated with the use of TMP-SMX in patients without AIDS are rare. These include anaphylaxis, severe cutaneous eruptions (Stevens-Johnson syndrome), and hematologic effects such as thrombocytopenia, leukopenia, and hemolytic anemia. TMP-SMX should not be given to patients with documented deficiency of folic acid or glucose-6-phosphate dehydrogenase.[4,19]

A much higher frequency of adverse reactions (up to 70%) such as skin rashes, blood dyscrasias, and hepatotoxicity has been reported in patients with AIDS.[3]

Teratogenic Risk

Trimethoprim is classified as a Category C agent. Since it may interfere with folic acid metabolism, use during pregnancy is indicated only if the potential benefit outweighs the potential risk to the fetus. It is recommended to avoid its use in the first trimester of pregnancy.[20]

Dosing Recommendations

TMP-SMX is currently available as Bactrim® by Roche, Septra® by Glaxo Wellcome, Cotrim® by Lemmon, and in generic form by numerous manufacturers. It is available as a single strength (80 mg trimethoprim and 400 mg sulfamethoxazole) or double strength (160 mg trimethoprim and 800 mg sulfamethoxazole) tablet, liquid suspension (40mg TMP and 200mg SMX/5ml) or intravenous formulation.[4] Generic products provide approximately a 50% cost savings to the patient; however, many patients report that the grape-flavored brand name product tastes better than the generic ones.[21]

The recommended dosage regimen for children over two months of age for the treatment of UTIs, Shigellosis, and acute otitis media is 8 mg/kg TMP/ 40 mg/kg SMX per day given in two divided doses every 12 hours for ten days. Patients with significantly impaired renal function (creatinine clearance 15 to 30 ml/min) should receive one-half of the usual dosage regimen since sulfamethoxazole metabolites may accumulate. Patients receiving hemodialysis may be given one dose after each dialysis treatment. TMP-SMX is not recommended for patients with creatinine clearance values less than 15 ml/min who are not receiving dialysis.[4]

Treatment of PCP requires a higher dosing regimen of 15 to 20 mg/kg TMP-SMX and 100 mg/kg SMX per day in divided doses every 6 hours. The intravenous dose is the same as the oral dose. Prophylaxis dosing of PCP for children is 150 mg/m^2 TMP and 750 mg/m^2 SMX per day given orally in equally divided doses twice a day on three consecutive days per week. The total daily dose should not exceed 320 mg TMP and 1600 mg SMX.[4]

Summary

TMP-SMX remains an economical option for the treatment of many childhood infections, especially those caused by *Streptococcus pneumoniae* and beta-lactamase producing strains of *Haemophilus influenzae*. This drug combination is very well-tolerated by most children. The two most serious adverse reactions associated with its use, exfoliative dermatitis and bone marrow depression, are rare. Other advantages of TMP-SMX include its applicability to penicillin allergic patients, and its twice-a-day dosage schedule.[6]

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Pharmacology Literature Review

Ketogenic Diet Review

The role of ketogenic diets in the treatment of children with refractory seizure disorders remains controversial. Several reports have described clinically significant reductions in the number of seizures experienced by children after strict adherence to a ketogenic program. This review describes the studies and cases reported to date with this therapy, as well as steps for implementing a ketogenic regimen. Tallian KB, Nahata MC, Tsao C. Role of the ketogenic diet in children with intractable seizures. **Ann Pharmacother 1998;32:349-61**, accompanying editorial **Ann Pharmacother 1998;32:384-5.**

Phenytoin Concentrations in Neonates

The bioavailability of oral phenytoin in the neonatal population has been shown in previous studies to be considerably lower than in older children and adults. For this reason, the oral route has not been routinely used for phenytoin administration to infants. The authors of this study refute that belief. They report the results of a prospective study involving 20 premature neonates who received oral or IV phenytoin. There were no significant differences between the groups in either the mean daily dose required or the mean serum phenytoin concentration achieved. Further work is needed to replicate these results, but oral phenytoin would be a significant benefit over IV therapy in avoiding phlebitis and extravasation. Frey OR, von Brenndorff AI, Probst W. Comparison of phenytoin serum concentrations in premature neonates following intravenous and oral administration. **Ann Pharmacother 1998;32:300-3.**

Saline versus Heparin for Catheters in Infants

While numerous studies have demonstrated the equivalency of heparin and normal saline to maintain patency in indwelling peripheral catheters in adults and older children, the studies conducted in infants have been inconclusive. This double-blind, randomized study was conducted in 74 infants less than one year of age, using 24-gauge catheters. The authors found no significant differences between the groups in duration of catheter use or reasons for removal. Nelson TJ, Graves SM. 0.9% Sodium chloride injection with and without heparin for maintaining peripheral indwelling intermittent-infusion devises in infants. **Am J Health-Syst Pharm 1998;55:570-3.**

Withdrawal of Antiepileptics

This brief review covers the pros and cons of stopping antiepileptics in patients who have been seizure-free for a period of more than 2 years. The results of 11 clinical trials are described as well as prognostic factors for identifying patients most likely to tolerate antiepileptic withdrawal. Buna DK. **Pharmacotherapy 1998;18:235-41.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/27/98:

1. Rituximab (Rituxan®) was added to the formulary for the treatment of patients with refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.
2. Trovafloxacin (PO)/alatrofloxacin (IV) (both agents marketed as Trovan®) were also added to the formulary. Trovan® replaces levofloxacin.
3. The antiviral, valacyclovir (Valtrex®), was also added. This agent replaces famiciclovir, which was removed from the formulary.

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