

Sulfamethoxazole / Trimethoprim



Brand Name: Septra, Sulfatrim, Bactrim

Drug Description

Sulfamethoxazole-trimethoprim, also known as SMX-TMP or co-trimoxazole, is a synergistic fixed combination of sulfamethoxazole, an intermediate-acting antibacterial sulfonamide, and trimethoprim. Both sulfamethoxazole and trimethoprim are synthetic folate antagonists. [1]

HIV/AIDS-Related Uses

SMX-TMP was approved by the FDA on June 23, 1981.[2] Oral and parenteral forms of SMX-TMP are indicated as the primary agent in the treatment of *Pneumocystis carinii* pneumonia (PCP), an opportunistic infection in patients with HIV/AIDS, and as secondary prophylaxis of PCP in patients who have already had at least one episode of PCP. SMX-TMP is also indicated in primary prophylaxis of PCP for HIV-infected adults with a CD4 count less than or equal to 200 cells/mm³ or less than 20% of total lymphocytes, and for all children born to HIV infected mothers (beginning at 4 to 6 weeks of age). Subsequent prophylaxis for children may be determined by age-specific CD4 lymphocyte count.[3]

The U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) recommend that shortly after being diagnosed with HIV infection, all HIV infected individuals should be tested to detect latent infection with *Toxoplasma gondii*. All individuals who are seropositive for *Toxoplasma* IgG antibody and who have a CD4 T cell count less than 100 cells/mm³ are recommended to receive primary prophylaxis against toxoplasmic encephalitis. SMX-TMP is the drug of choice for primary prophylaxis of toxoplasmic encephalitis, and dosages recommended for prophylaxis against PCP appear to be effective against toxoplasmic encephalitis.[4]

Non-HIV/AIDS-Related Uses

SMX-TMP is indicated for the treatment of chronic bronchitis, enterocolitis caused by strains of *Shigella* (*flexneri* and *sonnei*), acute otitis media in children, traveler's diarrhea caused by enterotoxigenic *Escherichia coli* and *Shigella*

species, and bacterial urinary tract infections.[5]

Pharmacology

SMX-TMP's action is usually bactericidal; sulfamethoxazole is bacteriostatic and trimethoprim is bactericidal. SMX-TMP acts by sequentially inhibiting enzymes of two steps in the folic acid pathway. Sulfamethoxazole inhibits the formation of dihydrofolic acid from para-aminobenzoic acid and by inhibiting dihydrofolate reductase, while trimethoprim inhibits the formation of tetrahydrofolic acid from dihydrofolic acid. By inhibiting synthesis of tetrahydrofolic acid, the metabolically active form of folic acid, SMX-TMP inhibits bacterial thymidine synthesis.[6] Organism susceptibility to trimethoprim is more critical to the efficacy of SMX-TMP than is susceptibility to sulfamethoxazole. Many organisms that are resistant to sulfamethoxazole but susceptible or only moderately susceptible to trimethoprim show synergistic antibacterial response to SMX-TMP.[7]

SMX-TMP is rapidly and well absorbed from the gastrointestinal tract following oral administration.[8] [9] Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound, and metabolized forms; sulfamethoxazole also exists as the conjugated form. Peak serum concentrations (C_{max}) of 1 to 2 mcg/ml of trimethoprim and 40 to 60 mcg/ml of unbound sulfamethoxazole are reached 1 to 4 hours after a single oral dose containing 160 mg trimethoprim and 800 mg sulfamethoxazole. Following multiple dose administration, steady-state C_{max} of SMX-TMP are usually 50% greater than those obtained after single-dose administration of the drug. Following oral administration of the fixed-ratio combination preparation, the trimethoprim-sulfamethoxazole ratio of mean steady-state serum concentration is usually about 1:20. Mean steady-state C_{max} of approximately 9 and 105 mcg/ml of trimethoprim and sulfamethoxazole, respectively, are reached after IV infusion of 160 mg of trimethoprim and 800 mg of sulfamethoxazole every 8 hours in adults with normal renal function. Steady-state trough concentrations reached with this IV dose are approximately 6 mcg/ml for trimethoprim and 70

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Pharmacology (cont.)

mcg/ml for sulfamethoxazole.[10]

SMX-TMP is widely distributed into body tissues and fluids, including sputum, aqueous humor, middle ear fluid, prostatic fluid, vaginal fluid, bile, and cerebrospinal fluid (CSF); trimethoprim also distributes into bronchial secretions. Trimethoprim has a larger volume of distribution than does sulfamethoxazole. In adults, the apparent volume of distribution is 100 to 120 L for trimethoprim and 12 to 18 L for sulfamethoxazole. In patients with uninflamed meninges, trimethoprim and sulfamethoxazole concentrations in CSF are about 50% and 40%, respectively, of concurrent serum concentrations of the drugs. Trimethoprim and sulfamethoxazole concentrations in middle ear fluid are approximately 75% and 20%, respectively, and in prostatic fluid are approximately 200% and 35%, respectively, of concurrent serum concentrations of the drug. SMX-TMP readily crosses the placenta; amniotic fluid concentrations of trimethoprim and sulfamethoxazole are reported to be 80% and 50%, respectively, of concurrent maternal serum concentrations. SMX-TMP also distributes into breast milk; concentrations in milk of trimethoprim and sulfamethoxazole are approximately 125% and 10%, respectively, of concurrent maternal serum concentrations.[11]

SMX-TMP is in FDA Pregnancy Category C. There are no large, well-controlled studies on the use of SMX-TMP in pregnant women. No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratologic effects manifested mainly as cleft palate. The highest dose that did not cause cleft palate in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In some rabbit studies, increased fetal loss was associated with trimethoprim doses 6 times the human therapeutic dose. Because both sulfamethoxazole and trimethoprim may interfere with folic acid metabolism, SMX-TMP should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[12]

Approximately 44% of trimethoprim and 70% of sulfamethoxazole are bound to plasma proteins. The presence of sulfamethoxazole in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole. Trimethoprim and sulfamethoxazole have serum half-lives of approximately 8 to 10 hours and 10 to 13 hours, respectively, in adults with normal renal function. In adults with creatinine clearances of 10 to 30 ml/min and 0 to 10 ml/min, serum half-life of trimethoprim may increase to 15 and greater than 26 hours, respectively. In adults with chronic renal failure, the sulfamethoxazole half-life may be 3 times that in patients with normal renal function. Trimethoprim serum half-lives of about 7.7 and 5.5 hours have been reported in children less than 1 year of age and between 1 and 10 years of age, respectively.[13]

SMX-TMP is metabolized in the liver. Trimethoprim is metabolized to oxide and hydroxylated metabolites, and sulfamethoxazole is principally N-acetylated and also conjugated with glucuronic acid. Both drugs are rapidly excreted in urine via glomerular filtration and tubular secretion. In adults with normal renal function, approximately 50% to 60% of trimethoprim and 45% to 70% of sulfamethoxazole in an oral dose are excreted in urine within 24 hours. Approximately 80% of trimethoprim and 20% of sulfamethoxazole recovered in urine are unchanged drug. In adults with normal renal function, urinary concentrations of active trimethoprim are approximately equal to those of active sulfamethoxazole. Urinary concentrations of both active drugs are decreased in patients with impaired renal function. Only small amounts of trimethoprim are excreted in feces via biliary elimination. Trimethoprim and active sulfamethoxazole are moderately removed by hemodialysis.[14]

Adverse Events/Toxicity

The most frequent adverse effects of SMX-TMP are gastrointestinal effects (nausea, vomiting, anorexia) and sensitivity skin reactions (rash, urticaria), each reportedly occurring in about 3.5% of patients. The development of rash, sore throat, fever, pallor, arthralgia, cough, shortness of breath,

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Adverse Events/Toxicity (cont.)

purpura, or jaundice may be an early sign of a serious adverse reaction to SMX-TMP.[15]

The frequency of some SMX-TMP adverse effects, including rash (usually diffuse, erythematous, and maculopapular), fever, leukopenia (neutropenia), thrombocytopenia, hyperkalemia, hyponatremia, and increased serum aminotransferase concentration, is substantially higher in patients with AIDS than in other patients. These adverse effects have occurred in up to 80% of AIDS patients receiving the drug but generally have been reversible following discontinuation of SMX-TMP therapy. Glutathione deficiency in HIV infected patients and the resultant accumulation of reactive hydroxylamine metabolites of sulfamethoxazole may be involved in the increased risk for hematologic adverse effects, but this requires further study. Limited evidence suggests that white AIDS patients may be at greater risk of hematologic adverse effects than black AIDS patients, indicating that genetic factors may also be important. Overall, adverse effects are usually less severe in patients receiving the drug for prophylaxis of PCP, compared with those receiving SMX-TMP for treatment of the disease.[16]

Ingestion of the oral suspension and tablets may cause dizziness.[17] Severe skin and blood problems may be more likely in elderly patients taking SMX-TMP, especially if diuretics are being taken concurrently. Potential side effects include hypersensitivity, photosensitivity, blood dyscrasias, cholestatic hepatitis, pancreatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis, central nervous system toxicity, Clostridium difficile colitis, crystalluria, hematuria, goiter, thyroid function disturbance, interstitial nephritis, tubular necrosis, methemoglobinemia, rhabdomyolysis, and thrombophlebitis.[18]

Drug and Food Interactions

SMX-TMP oral suspension and tablets should be taken with a full glass of water.[19]

SMX-TMP may prolong the prothrombin time (PT) of patients receiving concomitant warfarin by inhibiting metabolic clearance of warfarin. If

SMX-TMP is used with warfarin, PT and warfarin dosage must be monitored carefully. Because SMX-TMP possesses anti-folate properties, the drug could theoretically increase the incidence of folate deficiencies induced by other drugs, such as phenytoin, when used concomitantly. Concomitant administration of usual dosages of SMX-TMP and phenytoin can increase the half-life of phenytoin by 39% and decrease the metabolic clearance rate of phenytoin by 27%. If the drugs are administered concomitantly, the possibility of an increased phenytoin effect should be considered.[20] In elderly patients concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura has been reported.[21]

Marked but reversible nephrotoxicity has been reported in renal transplant patients receiving concomitant SMX-TMP and cyclosporine. Increases in serum digoxin concentrations, especially in geriatric patients, can occur when SMX-TMP and digoxin are given concurrently. Increased plasma sulfamethoxazole concentration may occur in patients receiving concurrent indomethacin. Megaloblastic anemia has been reported in patients receiving SMX-TMP and pyrimethamine dosages exceeding 25 mg weekly for malaria prophylaxis. Concomitant administration of tricyclic antidepressants and SMX-TMP may decrease the efficacy of the antidepressant. Toxic delirium has been reported in one individual following administration of SMX-TMP and amantadine.[22]

Because sulfonamides can displace methotrexate from plasma protein binding sites and increase free methotrexate concentrations, SMX-TMP should be used with caution in patients receiving methotrexate. Like other sulfonamides, SMX-TMP potentiates the effect of oral hypoglycemic agents.[23]

Contraindications

SMX-TMP is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfamethoxazole or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. It is also contraindicated in pregnant patients at term and in nursing mothers

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Contraindications (cont.)

(sulfonamides pass the placenta, are excreted in the milk, and may cause kernicterus) and in pediatric patients less than 2 months of age.[24]

SMX-TMP shares the toxic potentials of sulfonamides and trimethoprim. Rarely, fatalities have occurred in patients receiving sulfonamides secondary to severe drug-induced reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such fatal reactions also have been reported when sulfonamides were used in fixed combination with other drugs (e.g., trimethoprim or erythromycin).[25] Sulfonamides, including the SMX-TMP combination, should be discontinued at the first appearance of skin rash or any sign of adverse reaction.[26]

Clinical Trials

For information on clinical trials that involve Sulfamethoxazole / Trimethoprim, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Sulfamethoxazole / Trimethoprim AND HIV Infections.

Dosing Information

Mode of Delivery: Oral; intravenous.[27]

Dosage Form: SMX-TMP oral suspension: sulfamethoxazole 200 mg/5 ml and trimethoprim 40 mg/5 ml.[28]

SMX-TMP oral tablets: sulfamethoxazole 400 mg and trimethoprim 80 mg; sulfamethoxazole 800 mg and trimethoprim 160 mg.[29]

SMX-TMP for intravenous administration: sulfamethoxazole 80 mg/ml and trimethoprim 16 mg/ml.[30]

Storage: SMX-TMP for intravenous injection should be stored at 15 C to 25 C (59 F to 77 F) or 15 C to 30 C (59 F to 86 F), depending on the formulation (follow manufacturers' recommendations) and should not be refrigerated.

Oral suspensions of SMX-TMP should be stored in tight, light-resistant containers at 15 C to 25 C (59 F to 77 F) or 15 C to 30 C (59 F to 86 F) depending on the formulation (follow manufacturers' recommendations). SMX-TMP tablets should be stored in well-closed, light-resistant containers at 15 C to 30 C (59 F to 86 F).[31]

Chemistry

CAS Name: Benzenesulfonamide, 4-amino-N-(5-methyl-3-isoxazolyl)-, mixt. with 5-((3,4,5-trimethoxyphenyl)methyl)-2,4-pyrimidinediamine[32]

CAS Number: 8064-90-2[33]

Molecular formula: Sulfamethoxazole: C10-H11-N3-O3-S; Trimethoprim: C14-H18-N4-O3[34]

Sulfamethoxazole: C47.42%, H4.38%, N16.59%, O18.95%, S12.66%; Trimethoprim: C57.92%, H6.25%, N19.30%, O16.53%[35]

Molecular weight: Sulfamethoxazole: 253.28; Trimethoprim: 290.32[36]

Physical Description: SMX-TMP contains a 5:1 ratio of sulfamethoxazole to trimethoprim. Potency of SMX-TMP is expressed in terms of trimethoprim content. Sulfamethoxazole occurs as a white to off-white, practically odorless, crystalline powder; trimethoprim occurs as white to cream-colored, bitter-tasting, odorless crystals or crystalline powder. Sodium hydroxide is added during the manufacture of SMX-TMP for injection concentrate to adjust pH to 10. SMX-TMP oral suspension has a pH of 5 to 6.5.[37]

Stability: SMX-TMP for injection should not be admixed with drugs or with solutions other than 5% dextrose, and solutions should not be refrigerated. Solutions containing 3.2 mg sulfamethoxazole and 0.64 mg trimethoprim per ml of 5% dextrose (1:25 dilution) are stable for 6 hours at room temperature. Solutions containing 3.2 to 4 mg of sulfamethoxazole and 0.64 to 0.8 mg trimethoprim per ml of 5% dextrose (1:20 dilution) are stable for 4 hours at room temperature. Solutions containing 4 to 5.3 mg of sulfamethoxazole and 0.8 to 1.1 mg

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Chemistry (cont.)

trimethoprim per ml of 5% dextrose (1:15 dilution) are stable for 2 hours at room temperature. Prior to infusion, solutions of the drug should be inspected visually and discarded if there is evidence of crystallization or cloudiness.[38]

Following initial entry into a multiple-dose vial of SMX-TMP for injection, the manufacturers recommend that the contents be used within 48 hours.[39]

Other Names

Cotrimoxazole[40]

Cotrimoxazol[41]

TMP-SMX[42]

Further Reading

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Manufacturer Information

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Sulfatrim
Alpharma, Inc.
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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