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 (Cmax) 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 Cmax 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 Cmax 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
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, fever, pallor, arthralgia, cough, shortness of breath,
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.
**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]

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
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


Manufacturer Information

Septra
King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620
(888) 840-5370

Sulfamethoxazole / Trimethoprim
King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, TN 37620
(888) 840-5370

Bactrim
Women First Healthcare
5355 Mira Sorrento Place - Suite 700
San Diego, CA 92121
(858) 509-1171

Sulfatrim
Alpharma, Inc.
One Executive Drive
Fort Lee, NJ 07024
(201) 947-7774

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
References

1. AHFS Drug Information - 2004; p. 420

2. FDA - Drugs Used to Treat Complications of HIV/AIDS. Available at: http://www.fda.gov/oashi/aids/stat_app.html. Accessed 01/18/05.

3. USP DI - 2004; p. 2583

4. AHFS Drug Information - 2004; p. 423

5. USP DI - 2004; p. 2583

6. AHFS Drug Information - 2004; p. 426

7. AHFS Drug Information - 2004; p. 426

8. AHFS Drug Information - 2004; p. 427


11. AHFS Drug Information - 2004; p. 428


13. AHFS Drug Information - 2004; p. 428

14. AHFS Drug Information - 2004; p. 428

15. AHFS Drug Information - 2004; p. 425

16. AHFS Drug Information - 2004; p. 425

17. USP DI - 2004; p. 2586

18. USP DI - 2004; p. 2584

19. USP DI - 2004; p. 2586

20. AHFS Drug Information - 2004; p. 426


22. AHFS Drug Information - 2004; p. 426

23. AHFS Drug Information - 2004; p. 426


25. AHFS Drug Information - 2004; p. 425


27. AHFS Drug Information - 2004; p. 428

28. AHFS Drug Information - 2004; p. 428

29. AHFS Drug Information - 2004; p. 428
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30. AHFS Drug Information - 2004; p. 428
31. AHFS Drug Information - 2004; p. 428


34. Merck Index - 2001; pp. 1589, 1730
35. Merck Index - 2001; pp. 1589, 1730
36. Merck Index - 2001; pp. 1589, 1730

37. AHFS Drug Information - 2004; p. 428
38. AHFS Drug Information - 2004; p. 428
39. AHFS Drug Information - 2004; p. 428