Sulfamethoxazole and trimethoprim injection is a combination of two antimicrobial agents. Sulfamethoxazole and trimethoprim are bacteriostatic agents that block two consecutive steps in the biosynthesis of nucleic acids, and in clinical infections as described in the following section.

Sulfamethoxazole and trimethoprim in combination are more effective than either agent alone in the treatment of Shigella (Shigella flexneri), Haemophilus influenzae (Haemophilus), and Staphylococcus aureus (Staphylococcus). Sulfamethoxazole and trimethoprim blocks two consecutive steps in the biosynthesis of nucleic acids when used in combination.

**Quality Control**

Quality control tests require the use of a bacterial control microorganism. Both sulfamethoxazole and trimethoprim should be used as recommended in the following table.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter Ranges (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em> ATCC 49247 tested by broth microdilution</td>
<td>8 to 15</td>
</tr>
</tbody>
</table>

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections (e.g., streptococcal pharyngitis or tonsillitis) without a proven or strongly suggested diagnosis. These infections should be treated with penicillin. If a patient with a penicillin allergy develops streptococcal infection (e.g., streptococcal pharyngitis or tonsillitis), therapy with sulfamethoxazole and trimethoprim should be reconsidered (see PRECAUTIONS).

**Pharmacokinetics**

**Absorption**

Sulfamethoxazole and trimethoprim are absorbed from the gastrointestinal tract in the fasted and fed state. Mean bioavailability is 96% following oral administration. Sulfamethoxazole is rapidly absorbed after intramuscular or intravenous administration.

**Distribution**

Sulfamethoxazole and trimethoprim distribute to sputum and vaginal fluid; trimethoprim also distributes to bronchial secretions, and both penetrate the placenta. In general, sulfamethoxazole and trimethoprim are also distributed to most body fluids, including saliva, bronchial secretions, synovial fluid, amniotic fluid, and cerebrospinal fluid (CSF). Their penetration into these fluids is enhanced in the presence of gram-negative pathogens.

**Metabolism**

Sulfamethoxazole and trimethoprim are almost completely absorbed from the gastrointestinal tract and distribute to most body fluids. Sulfamethoxazole and trimethoprim are excreted into the bile by the process of active sodium-dependent resorption. A portion of sulfamethoxazole is then reabsorbed back into the systemic circulation. The reabsorbed sulfamethoxazole is then excreted into the urine.

**Adverse Reactions**

Sulfamethoxazole and trimethoprim should be used with caution in patients with porphyria or thyroid disorders. Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Contraindications**

Sulfamethoxazole and trimethoprim injection is contraindicated in patients who have had a previously severe reaction to sulfamethoxazole or trimethoprim. Sulfamethoxazole and trimethoprim are also contraindicated in patients with drug-induced porphyria or a history of porphyria.

**Warnings**

**Hypoglycemia**

Patients with diabetes mellitus and those receiving anticonvulsant therapy may develop hypoglycemia when treated with sulfamethoxazole and trimethoprim. Patients with diabetes mellitus should be closely monitored for signs of hypoglycemia.

**Renal//Hepatic Impairment**

Sulfamethoxazole and trimethoprim are primarily eliminated by the kidneys. Patients with severe renal impairment are at increased risk of sulfamethoxazole and trimethoprim toxicity. The use of sulfamethoxazole and trimethoprim in patients with severe renal impairment should be monitored closely.

**Hematological Changes**

Sulfamethoxazole and trimethoprim are known to cause a variety of hematological changes, including hemolytic anemia, agranulocytosis, thrombocytopenia, and aplastic anemia. These changes may be reversible with discontinuation of sulfamethoxazole and trimethoprim.

**Sulfite Sensitivity**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Information for Patients**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Pregnancy**

Sulfamethoxazole and trimethoprim injection is contraindicated in women who are or may become pregnant. Sulfamethoxazole and trimethoprim injection is excreted in breast milk and is not recommended for use in nursing women.

**Nursing Mothers**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Pediatric Use**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Geriatric Use**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.

**Adverse Reactions**

Sulfamethoxazole and trimethoprim injection contains sodium metabisulfite, a sulfite that may cause an anaphylactoid reaction in patients who have demonstrated a sensitivity to sulfites.
In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was seen. In rats, oral doses of 533 mg/kg or 200 mg/kg produced teratologic effects manifested mainly as skeletal anomalies. In addition, in a separate study involving rats, oral gavage dosages as high as 350 mg/kg/day sulfamethoxazole plus 70 mg/kg/day trimethoprim. No adverse effects on fertility or general reproductive performance were observed in rats given oral sulfamethoxazole and trimethoprim. Observations of leukocytes obtained from patients treated with sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate method used to measure methotrexate. Methotrexate is measured by a radioimmunoassay (RIA).

In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of hyperkalemia has been reported. Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with methotrexate therapy. In one study, sulfamethoxazole increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 25%. In elderly patients, the risk of hyperkalemia is increased when sulfonamide and diuretic therapy are combined. The presence of sulfamethoxazole and trimethoprim may also interfere with the Jaffé alkaline picrate method used to measure methotrexate. Methotrexate is measured by a radioimmunoassay (RIA).

Of note, the maximum tolerated dose in humans is unknown. Signs and symptoms of overdosage reported in volunteers are: abdominal pain, diarrhea, anorexia.

In the literature, three cases of hyperkalemia in elderly patients have been reported after concomitant use of oral sulfamethoxazole and trimethoprim and amantadine. Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with methotrexate therapy. In one study, sulfamethoxazole increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 25%.


ADVERSE REACTIONS

Nursing Mothers

Sulfamethoxazole and trimethoprim injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There is no information regarding the use of sulfamethoxazole and trimethoprim injection in pregnant women. In animal reproduction studies, sulfamethoxazole and trimethoprim did not cause an increased incidence of congenital abnormalities. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral sulfamethoxazole and trimethoprim at the time of conception or shortly thereafter.

At least 186 pregnancies during which the mother received either placebo or sulfamethoxazole and trimethoprim were reported. The overall incidence of congenital abnormalities in this group was 2.9% (6 of 186) compared to 3.2% (4 of 125) in those receiving placebo. There were no statistically significant differences between the treatment groups in the incidence of congenital abnormalities. Placebo-controlled trials in pregnant women are needed to determine whether there is an increased incidence of congenital abnormalities in infants of mothers receiving sulfamethoxazole and trimethoprim injection during pregnancy.

Allergic Reactions

Malignant Lymphoma

Malignant lymphoma, particularly of the Hodgkin type, has been reported in association with trimethoprim-sulfamethoxazole therapy. The mechanism in each case was not established and it was not possible to determine whether trimethoprim-sulfamethoxazole was the causal agent. Cases of lymphoma have occurred in heterogeneous groups of patients including children and adults, with and without underlying disease, and following long or short courses of treatment. In all cases, malignancy developed after therapy with trimethoprim-sulfamethoxazole.

Neoplasia

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with sulfamethoxazole and trimethoprim. In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was seen. Among the malignancies that have been reported more frequently in patients receiving trimethoprim-sulfamethoxazole as compared to controls were testicular tumors in male rats.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and chlorothiazide), and anti-infectives (dapsone, dapsone-like compounds, antimalarials, and tetracyclines). None of these compounds have been shown to cause goiter. However, because the sulfonamides may elicit this type of response, careful monitoring of thyroid function is recommended when the sulfonamides are used in patients with impaired thyroid function. The sulfonamides are capable of inhibiting the Jaffé reaction used to measure serum bilirubin, and of displacing bilirubin from albumin. Bilirubinemia may also occur in association with severe infections. Therefore, one should carefully monitor patients for jaundice while receiving trimethoprim-sulfamethoxazole therapy.

The trimethoprim component of sulfamethoxazole and trimethoprim may cause hyperkalemia when used as a hyperkalemic diuretic. The trimethoprim component may also cause hyperkalemia when used as a potassium-sparing diuretic. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for the hematologic or hepatic defect.

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