Dapsone



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Mechanism

Inhibits Dihydropteroate Synthase
Inhibiting-chains on Two-headed-pterodactyl with Synthase-taser
Dapsone is a competitive agonist of Dihydropteroate Synthase, an enzyme important in folate synthesis. It inhibits this enzyme by competing with PABA for the active site of Dihydropteroate Synthase. This prevents normal bacterial utilization of PABA in the synthesis of folic acid. In short, Dapsone makes it so bacteria cannot make folic acid which results in a depletion of the folate pool, and a reduction in the amount of thymidylate available for DNA synthesis. Thus, bacteria that are deprived of folate will eventually die.

Structural Analog of PABA
PABA-bear on a Log
Dapsone is a structural analog of para-aminobenzoic acid (PABA), and competes with para-aminobenzoic acid (PABA) for incorporation into folic acid. The incorporation of Dapsone causes inhibition of the enzyme dihydropteroate synthase in the folic acid synthesis pathway. Because folic acid is necessary for vital cell functions like DNA synthesis, bacteria that are deprived of folate will eventually die.

Similar to Sulfonamides
Sulfur-match-fondue
The mechanism of action of Dapsone is similar to sulfonamides, another class of antibiotics. The incorporation of sulfonamides also causes inhibition of the enzyme dihydropteroate synthase in the folic acid synthesis pathway. While the mechanism may be similar, it is important to remember that Dapsone is structurally distinct. Dapsone does have a sulfa moiety and is known as a sulfone. This distinction is important to consider in a patient with a history of sulfa allergies, as there may be some cross-reactivity.

Impairs Folic Acid Synthesis
Impaired Flicking Acidic-lemon
Dapsone is a competitive agonist (inhibits) Dihydropteroate Synthase, an enzyme important in folate synthesis in bacteria. Inhibition of this enzyme results inhibition of folate synthesis, depletion of the folate pool, and a reduction in the amount of thymidylate available for DNA synthesis. This eventually results in bacterial cell death.

Indications

Leprosy
Leopard
Leprosy, or Hansen's disease, is a chronic, infectious disease caused by Mycobacterium leprae. There are two forms of leprosy: tuberculoid, the less severe form, and lepromatous, the more severe form primarily seen in the immunocompromised. Dapsone is used as part of multi-drug therapy in the treatment of leprosy, often in combination with rifampin and/or clofazimine.

Pneumocystis jirovecii
Nude-Mona-sisters in a Jeep
Pneumocystis jirovecii is a yeast that typically causes lung infection in immunocompromised patients. Trimethoprim-sulfamethoxazole is the first-line line agent for the prevention and treatment of Pneumocystis jirovecii pneumonia. However, in some situations, this medication cannot be used, and dapsone is

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considered a second-line agent.

Dermatitis Herpetiformis

Herb-head with Rash

Dermatitis herpetiformis is an autoimmune, blistering, cutaneous condition linked to celiac disease. Despite its name, this condition is not associated with herpes. Although a gluten-free diet is the first-line treatment for dermatitis herpetiformis, sometimes diet modification is not enough or not an option for patients. Dapsone is the only FDA-approved drug used in the treatment of dermatitis herpetiformis. The mechanism of action of Dapsone in dermatitis herpetiformis is related to its effects on neutrophil function and recruitment. Patients typically respond well to Dapsone, typically with pruritis improving in 1-2 days and blisters improving within 1 week.

Adverse Effects

Hemolysis in G6PD Deficient Patients

Hemolysing RBCs coming out of Glue-(6)Sax-P-Dehydrator

Dapsone's metabolite, hydroxylamine, can cause increased oxidative stress in the body. Increased oxidative stress precipitates hemolytic anemia in individuals with G6PD deficiency. Glucose 6 phosphate dehydrogenase deficiency is an X-linked recessive disorder characterized by a deficiency of the enzyme glucose 6 phosphate dehydrogenase (G6PD). This enzyme is involved in the pentose phosphate pathway and supplies reducing substances by converting NADP to NADPH. This NADPH is used by glutathione reductase to maintain levels of glutathione in cells, which helps protect red blood cells against oxidative damage caused by free radicals and peroxides.

Methemoglobinemia

Moth-He-man-globe

Methemoglobin is a variant of hemoglobin with decreased ability to bind oxygen (causes a leftward shift in the oxygen dissociation curve). It is formed when ferrous irons (Fe2+) within the heme moiety are oxidized to ferric irons (Fe3+). Methemoglobinemia occurs when the concentration of methemoglobin increases from physiologic levels. This increase can severely limit oxygen delivery to tissues and can be life-threatening. Dapsone is metabolized into potent oxidants, such as hydroxylamine. Oxidants are responsible for Dapsone's hematologic effects, namely hemolytic anemia and methemoglobinemia. Dapsone is the medication that most commonly causes methemoglobinemia. Other offending drugs include local anesthetics such as lidocaine and benzocaine.

Agranulocytosis

A-granny-side-toe

Agranulocytosis is a condition in which the absolute neutrophil count is extremely low. Rarely, Dapsone can cause agranulocytosis in patients. There are several proposed mechanisms for this. Most implicate hydroxylamine, a metabolite of Dapsone and potent oxidant, and involve either bone marrow suppression or direct action on neutrophils and their maturation. Regardless, agranulocytosis is a documented side effect of Dapsone to be aware of. Other drugs that can cause agranulocytosis include clozapine, anti-thyroid agents, and sulfonamides.

Peripheral Neuropathy

Purple-wavy Neuron-extremities

Peripheral neuropathy is a rare complication of oral dapsone therapy. Motor loss is predominant. The mechanism of this adverse effect is still under debate. The most popular theory suggests direct neurotoxicity, as Dapsone can concentrate in neural tissue. The onset of peripheral neuropathy after initiation of oral dapsone therapy is variable. Additionally, the dose of Dapsone that results in peripheral neuropathy is variable. If muscle weakness is reported, Dapsone should be stopped immediately. Recovery upon withdrawal of Dapsone is variable, and there is a potential for long-term persistence.

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