CHAPTER 16

DAPSON TREATMENT IN DERMATOLOGY

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HISTORY

The story of dapsone also began long ago. Sulfonamides were first derived from coal tar in the early 1900s for use as fabric dyes. This sulfone was synthesized in Germany in 1908, even though there was no interest in any possible therapeutic application until 1932, when the German Gerhardt Domagk discovered the antibacterial action of sulfones and of sulfonamide.[1] Medically, they were first demonstrated to be effective against streptococcal infections. (bolognia) Dapsone was introduced in India at the end of the Second World War by the Englishman Robert Greenhill Cochrane to treat leprosy.[3] It proved it self to be the first drug to show efficacy in this disease. Later, the usefulness of dapsone in treating malaria and *Pneumocystis jirovecii* pneumonia in AIDS patients was established.[4]

Dapsone clearly has dual functions of both: antimicrobial/antiprotozoal effects and anti-inflammatory features similarly to non-steroidal anti-inflammatory drugs. The latter capabilities primarily were used in treating chronic inflammatory disorders.[5]

The related drugs sulfapyridine and sulfoxane were used in the first half of the twentieth century to treat dermatitis herpetiformis (DH). It was subsequently used in the therapy of some dermatoses, in particular those bullous dermatoses and vasculitic syndromes characterized by infiltration of granulocytes and neutrophils, from which comes the influx at the lesion level.[6]

Further research into sulfonamides resulted in the development of the first commercially available antibiotic, prontosil, a closely related chemical compound. Dapsone discovery led to a Nobel Prize for the creator and unprecedented interest in the development and use of sulfa compounds in the 1930s and 1940s.[7]

Dapsone's use in the treatment of rheumatic disease, introduced in various contexts in the 1970s and 1980s, is not particularly widespread, above all for the incidence of undesirable side effects, some which are quite serious, such as metemoglobinemia, even though its efficacy in bullous SLE eruptions has been confirmed,[(8)] and in particular in recurrent polychondritis.[9]

CHEMISTRY AND PHARMACOLOGY

Dapsone (4,4-diaminodiphenylsulfone, DDS,) is an aniline derivative incoporating a sulfone molecule but has unique pharmacologic properties. As a sulfone, it shows the structure of a sulphur atom linking to two carbon atoms (Figure 1). While its antimicrobial role involves competitive inhibition of para-aminobenzoic acid, dapson has a wide variety of actions, including down-regulating leukotriene B4 synthesis as well as neutrophil and lymphocyte function.

Although dapsone has many associated pharmacologic and idiosyncratic adverse events, a complete understanding of the drug's pharmacology, as well as proposed mechanisms of action and potential adverse events, will allow the clinician to use dapsone in a manner that maximizes the therapeutic benefit and minimizes the likelihood of significant adverse effects.[4]

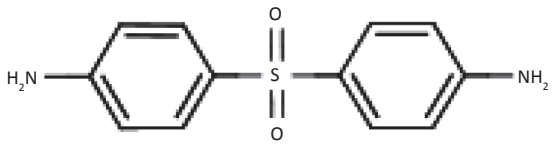


Figure 1. The structure of dapsone

ABSORPTION/ BIOAVAILABILITY/ METABOLISM/ EXCRETION

Dapsone has highly lipophilic nature and water-insoluble compound that penetrates exellent into cells and various tissues. Dapsone is 80% bioavaliable, peaks in the serum between 2-6 hours post-administration, with approximately 70% of the drug bound to plasma protein and has a half-life of 24-30 hours.[2] In a steady-state condition 100 mg of dapsone results in a mean level at 24 hours of 1.95 mg/L, with a peak of approximately 3 mg/L occurring 2-6 hours after an oral dose.[10]

Dapson and its major metabolite mono-acetyldapsone (MADDS) are strongely protein bound and undergo enterohepatic recirculation. This long elimination half-life results in dapsone remaining in the circulation for as long as 30 days after a single oral dose.[11]

even glucose-6-phosphate dehydrogenase (G6PD)-deficient patients can use dapsone gel safely, contrary to initial concerns.[106-111]

CONTRAINDICATIONS

Dapsone is contraindicated in patients with documented hypersensitivity to the drug. It is important to note, however, that cross-sensitivity between dapsone and sulfapyridine or other sulfonamide-type drugs is quite rare, even in HIV-infected patients with documented trimethoprim/sulfamethoxazole allergy. Topical dapsone has not shown any cross-reactivity in sulfonamide-allergic patients. A relative contraindication to the use of both drugs is related to the pharmacologic adverse events. In patients at increased risk for the development of the pharmacologic adverse effects due to pulmonary, cardiovascular, or hematologic disease, including G6PD deficiency, great care should be taken in treatment with dapsone.[112,113].

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