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Dapsone

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1. DESCRIPTION

Dapsone (4,4′-diaminodiphenylsulfone; DDS) is a sulfone that was the first effective antimicrobial for the treatment of leprosy. It has since been found useful in the treatment and prevention of malaria, *Pneumocystis jiroveci infection,* and *Toxoplasma gondii* infection. Its immunomodulatory effects have been found beneficial in a number of noninfective dermatologic and other inflammatory disorders.

Dapsone synthesis from *p*-nitrothiophenol was first described by Fromm and Wittman in 1908; however, its antimicrobial properties were not fully appreciated until the successful treatment of streptococcal infections in mice was reported by Buttle *et al.* in 1937. Soon after, reports of its efficacy against *Mycobacterium leprae* were published (Cowdry and Ruangsiri, 1940). The history of the discovery of dapsone has been well described (Doull, 1963; Wozel, 1989; Barr, 2011). By the end of the 1940s, dapsone had revolutionized the treatment of leprosy, hastening the closure of leprosariums around the world.

Dapsone is a sulfone, a folic acid antagonist that, like the sulfonamides, inhibits folic acid synthesis. It acts as a competitive inhibitor of dihydropteroate synthase (DHPS), preventing the normal utilization of *p*-aminobenzoic acid. It was initially used as a number of dapsone prodrugs such as acedapsone; however, they soon fell out of use as experience with dapsone evolved. It is currently available as an oral and topical formulation.

The molecular structure of dapsone is shown in Figure 94.1.

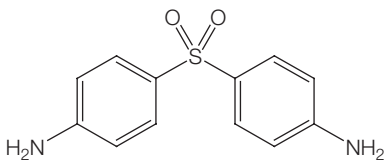

Figure 94.1. Molecular structure of dapsone (4-4′ diaminodiphenylsulfone).

2. ANTIMICROBIAL ACTIVITY

2a. Routine susceptibility

Dapsone, like other sulfones and sulfonamides, has a broad spectrum of activity against many bacteria and protozoans. However, owing to early experience with drug toxicity at the doses that were foreseen as necessary against common bacteria, development in this direction did not continue. Lowe (1950) reported a personal communication by Buttle that a therapeutic trial in humans at a dose of 1–2 g/day was abandoned early because of the development of acute toxicity (Lowe, 1950). The literature has practically been devoid of papers describing dapsone's *in vitro* activity against common bacterial pathogens. One exception describes the activity of dapsone alone and *in vitro* synergy between dapsone and trimethoprim against methicillin-resistant *Staphylococcus aureus* (MRSA). Sixty isolates of MRSA were tested by use of the broth microdilution method, and all were found to have minimum inhibitory concentrations (MICs) ranging from 16 to 2056 μg/ml—regarded as resistant, because these levels are generally unachievable with normal dosing. When tested in combination with trimethoprim, 50% of strains were found to be susceptible at a 1:19 and 1:1 ratio of trimethoprim to dapsone. Given the high level of penetration in the skin and its long half-life, it was hypothesized that the combination may have uses in the eradication of the staphylococcal carrier state (Lambertus *et al.,* 1990). No trials have subsequently been reported.

MYCOBACTERIUM LEPRAE

M. leprae is exquisitely susceptible to dapsone. Given that the organism could not be cultivated *in vitro,* animal models of the disease were first to show a response to dapsone therapy (Cowdry and Ruangsiri, 1940), soon after followed by human trials. *M. leprae* has an MIC that is estimated to be on the order of 3.0 ng/ml (3.0 μg/l) and at that level is regarded as weakly bactericidal (World Health Organization [WHO], 1982). The method by which susceptibility testing of *M.*