Innovative Use of Dapsone

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KEYWORDS

• Dapsone • Dermatology • Sulfone

In the past, sulfones were used preferentially as antimicrobial/chemotherapeutic agents to treat infections caused by streptococcus, mycobacteriaceae, and other bacteria.[1] Currently, dapsone (4,4′ diaminodiphenylsulfone) is the only remaining sulfone congener used in human therapeutics. Because of its dual mechanism of action—antimicrobial and anti-inflammatory/immunomodulatory effects—dapsone alone or in conjunction with other drugs is used worldwide for preventing and treating pathogen-caused diseases (eg, leprosy, *Pneumocystis jiroveci* pneumonia in individuals with HIV infection) or chronic inflammatory diseases, especially in the field of dermatology (eg, autoimmune bullous eruptions).

Synthesis of dapsone was reported in 1908 by Emil Fromm (**Fig. 1**), professor of organic chemistry in Freiburg/Germany, and Jakob Wittmann during their experiments in dye chemistry.[2] When first synthesized, dapsone was not envisioned as a medical agent. In 1937, soon after the discovery of sulphonamides as antibiotics, two research groups (one in England and one in France) were the first to investigate dapsone. Both groups concurrently published the observed anti-inflammatory potency of dapsone in experimentally induced infections in mice.[3,4] In the narrowest sense, that marked the beginning of the sulfone story.

From a historical perspective, it is remarkable that other sulfones, and not the so-called "parent sulfone" (dapsone), were first used to treat gonorrhoea.[5,6] After extensive use of with promin and related sulfones in the treatment of Hansen's disease at the U.S. leprosarium in Carville, Louisiana early in the 1940s by Faget and coworkers,[7] sulfones ultimately developed from simple chemical compounds into valuable therapeutic agents.

In 1950, the Portuguese Esteves and Brandão[8] introduced sulfones (eg, Sulphetrone, Diasone) into dermatology through their reports of their successful use in treating dermatitis herpetiformis (Duhring's disease), which was subsequently confirmed by other groups.

Later, Sneddon and Wilkinson[9] in England reported a remission in subcorneal pustulosis after dapsone administration. Since that time, dapsone has been increasingly considered effective in treating neutrophil-mediated processes and autoimmune skin diseases, and retains its place in the therapeutic armamentarium as a unique and essential agent.

CHEMISTRY AND PHARMACOLOGY

Chemically, dapsone is an aniline derivative. All sulfones share the structure of a sulfur atom linking to two carbon atoms (**Fig. 2**). The solubility of dapsone varies over a large range depending on the solvent used (eg, water, 0.2 mg/mL, methanol, 52 mg/mL). Dapsone has been considered a difficult-to-handle compound for experimental investigations, especially using living cell assays.[10]

After oral administration, dapsone is almost completely absorbed from the gastrointestinal tract with bioavailability of more than 86%. Peak serum concentrations are generally attained within 2 to 8 hours. After ingestion of a single 50- to 300-mg dose of dapsone, maximal serum concentrations are reached between 0.63 and 4.82 mg/L.[10–12] Under steady-state conditions, the most frequently used dosage of 100 mg/d

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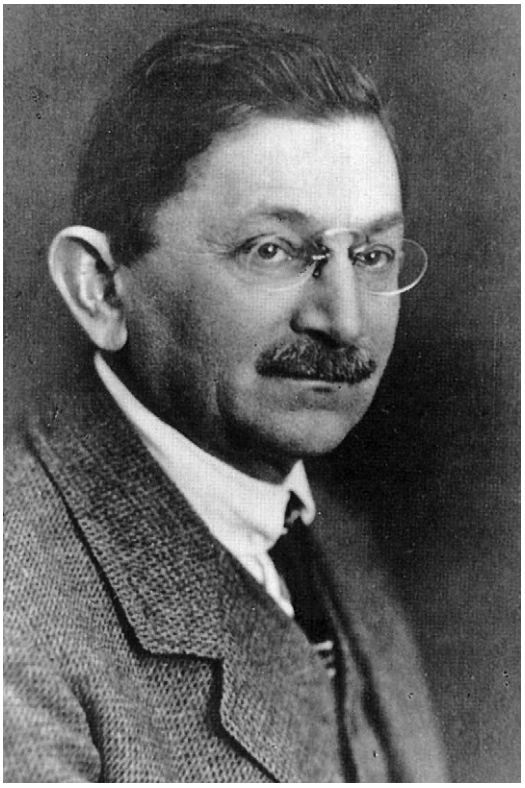

Fig. 1. Emil Fromm (1865–1928). (*Courtesy of* Institut für Geschichte der Medizin der Universität Wien; with permission.)

results in serum concentration of 3.26 (maximum) and 1.95 mg/L (after 24 hours).[13] These dapsone serum concentrations, attainable in vivo, must be strictly considered when interpreting the results of in vitro investigations.

After absorption, dapsone undergoes enterohepatic circulation. It is metabolized both by the liver and activated polymorphonuclear leucocytes (PMN) or mononuclear cells.[14] In the liver, dapsone is metabolized primarily through acetylation by *N*-acetyltransferase to monoacetyldapsone (MADDS), and through hydroxylation by cytochrome P-450 enzymes, resulting in

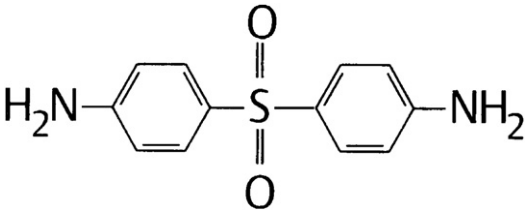

Fig. 2. Structural formula of dapsone (4,4′ diaminodiphenylsulfone).

generation of dapsone hydroxylamine (DDS-NOH) (**Fig. 3**). Acetylation is genetically determined, resulting in significant variability in acetylation (rapid or slow acetylator). In fact, dapsone can be administered to determine the acetylation phenotype.

In terms of both efficacy and induction of adverse effects, the most important factor is the generation of DDS-NOH; this occurs in lesional inflammatory processes in skin mediated by activated PMN.[14] Dapsone is distributed to all organs, crosses the blood–brain barrier and placenta, and is detectable in breast milk.[15,16] Approximately 20% of dapsone is excreted in urine as unchanged drug and 70% to 85% as water-soluble metabolites. Additionally, a small amount may be excreted in feces. The complex metabolic pathway of dapsone has been reviewed in detail several times.[10,12,14,17,18]

MECHANISM OF ACTION

The therapeutic efficacy most likely is based on differing drug activities when considering pathogen-caused diseases and noninfectious dermatologic disorders (**Fig. 4**). Antimicrobial activity is usually bacteriostatic in nature and seems to mimic that of sulfonamides (inhibition of folic acid synthesis in susceptible organisms), because antibacterial activity is inhibited by para-aminobenzoic acid.

When used as therapy for inflammatory disorders, however, alternate mechanisms are at work. Recent investigation shows that dapsone alone (and through its metabolites) has similarities to nonsteroidal anti-inflammatory drugs (NSAIDs).[10] However, these data were obtained through varying methods and under different experimental conditions. These discrepancies raise some important questions, such as which types of investigations render the most valid data for human use: in vitro versus in vivo investigation, animal versus human model, or single administration versus steady-state administration.

Additionally, several investigations have evaluated the capability of dapsone to ameliorate or block specific pathways using drug concentrations that are not achieved in humans. Therefore, despite many experimental investigations using dapsone, the relevance of observed effects remains unclear. This problem is even more obvious because the pathogenesis of dapsone-sensitive dermatoses has not been fully elucidated.

The ability of dapsone to inhibit reactive oxygen species (ROS) seems to contribute to the drug's anti-inflammatory effects.[19] ROS can be generated through two major pathways: the PMN-mediated