Innovative Use of Dapsone

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• 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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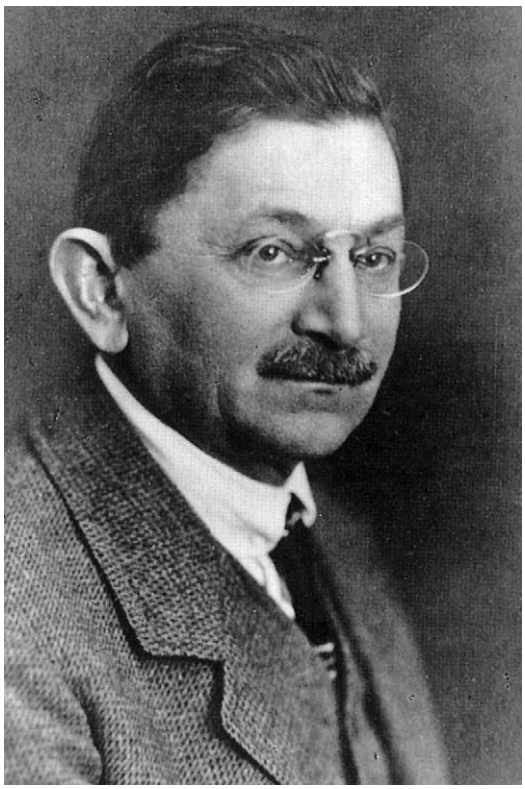
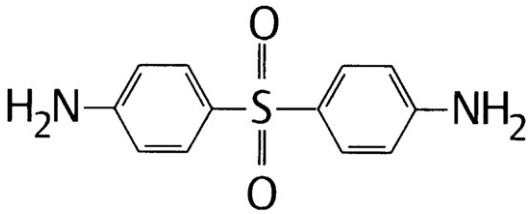


Fig. 1. Emil Fromm (1865–1928). (*Courtesy of* Institut für Geschichte der Medizin der Universität Wien; with permission.)

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



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

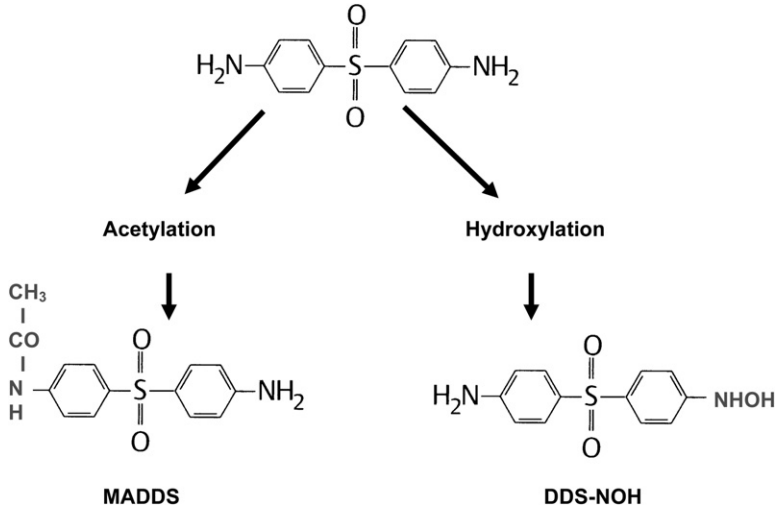
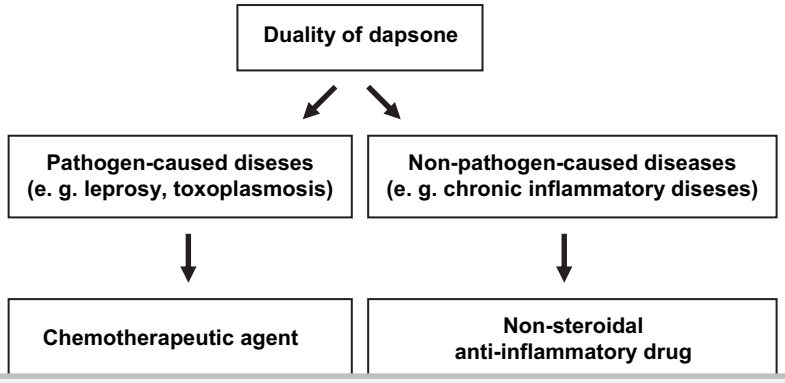


Fig. 3. Main metabolic pathway of dapsone. MADDS, monacetyl dapsone; DDS-NOH, dapsone hydroxylamine.

intracellular system and an extracellular xanthine/xanthine–oxidase system. Both are affected by dapsone to the same extent.[20]

Niwa and colleagues[20] showed that dapsone has a scavenger-like effect; it quenches all ROS except the oxygen intermediate, O_2^-. Although Stendahl and colleagues[21] ascribed the depression of cytotoxic and cytopathic functions of PMNs to the ability of dapsone to directly inhibit the myeloperoxidase (MPO)–H_2O_2–halide system, it may also be caused by the marked decrease in hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and oxygen (O_2) levels as a result of scavenger-like functions of dapsone. The cytotoxic potency in the MPO–H_2O_2–halide system may not be highly powerful, because patients with MPO deficiency are not unduly susceptible to infections.

Being one of the strongest scavengers known, dapsone decreases H_2O_2 as effectively as catalase and is as potent as colchicine, superoxide-dismutase, catalase, benzoate, and xanthine in lowering OH levels. Severe tissue injury observed in patients with disorders such as dermatitis herpetiformis, linear IgA bullous dermatosis, prurigo pigmentosa, leukocytoclastic vasculitis, Behçet's disease, and lupus erythematosus (LE) must be considered partly as a consequence of excessive PMN-generated oxygen intermediates.[20,22,23] The beneficial effects of dapsone on these dermatologic disorders are most likely a result of its quenching effects. Whether O_2^- and OH concentrations are linked by an iron-dependent mechanism is still unknown.



Several reports indicate that dapsone may also affect additional inflammatory effector systems through

- Suppression of integrin-mediated neutrophilic adherence[24]
- Inhibition of generation of 5-lipoxygenase products (eg, leukotriene B_4 [LTB_4], 12-hydroxyeicosatetrenoate [HETE])[25]
- Inhibition of spontaneous or induced synthesis of prostaglandin E_2[26]
- Inhibition of cyclooxygenase I– and II–mediated generation of thromboxane B_2[27]
- Interference with activation or function of the G-protein, resulting in an inhibition of signal transduction[28]
- A protective effect on α1-protease inhibitor[29]
- Inhibition of cysteinyl leukotrienes (leukotriene C_4)[30]
- Inhibition of LTB_4 receptor binding of human PMN[31]
- Inhibition of interleukin (IL)-8 production/releasing of peripheral blood stimulated with lipopolysaccharide[32]
- Inhibition of mitogen-induced lymphocyte transformation.[33]

Moreover, it has been shown that dapsone has neuroprotective effects against quinolate- and kainate-induced striatal neurotoxicities in rats and attenuates kainic-induced seizures in rats.[34–36]

Summarizing these diverse mechanisms, growing evidence shows that dapsone is considered to be a pharmacodynamically active compound. The anti-inflammatory capacity of dapsone is generally attributed to the parent compound. The authors therefore addressed the question as to whether the two major dapsone metabolites (MADDS and DDS-NOH) possess anti-inflammatory properties of their own. High performance liquid chromatography analysis of 5-lipoxygenase products from calcium ionophore–stimulated isolated PMN showed that DDS-NOH is one magnitude more effective than dapsone and MADDS in suppressing the generation of LTB_4 and 5-HETE (eg, IC_{50} LTB_4: DDS-NOH, 0.490 μmol; dapsone, 15 μmol; MADDS, 40 μmol). Moreover, determination of lucigenin- and luminal-enhanced chemiluminescence of zymosan-stimulated human whole blood and isolated PMN showed that DDS-NOH (0.1–100 μmol) causes a significant and dose-dependent inhibition of oxidative burst, leading to almost complete suppression at the highest concentration tested.[37] Again, DDS-NOH was more effective than dapsone or MADDS.

After topical pretreatment with MADDS and

weeks, 10 ng LTB_4 were applied on the upper arm skin of eight healthy volunteers. Biopsies were taken after 24 hours and PMNs were quantified fluorometrically using elastase as a marker enzyme. MADDS did not show any inhibitory activity on PMN trafficking compared with the corresponding control and nontreated area (untreated: 790 ± 450 PMN per 10 μg skin; $P>.05$, acetone: 840 ± 578 PMN per 10 μg skin; MADDS: 1099 ± 556 PMN per 10 μg skin), whereas DDS-NOH caused a statistically significant inhibition of PMN accumulation, as did the reference clobetasol-17-propionate (CP) (DDS-NOH: 128 ± 143 PMN per 10 μg skin; CP: 86 ± 131 PMN per 10 μg skin; $P<.01$).[38] These results again indicate that only DDS-NOH can inhibit LTB_4-induced accumulation of PMN in healthy individuals.

In line with these in vivo experiments are results with dapsone, MADDS, and DDS-NOH to determine their effect on ultraviolet (UV)-induced erythema. Skin areas were irradiated with UVB (295 nm, two minimal erythema doses). Twenty-four hours later, UVB-induced erythema was quantified using the CR-200b handheld Chroma Meter (Minolta, Osaka, Japan) and cutaneous blood flow was measured using a Moor Laser Doppler Imager (Moor Instruments, Devon, England). In control skin, tissue blood flow was measured to be 227 units and was significantly ($P<0.05$) decreased by dapsone (186 units), DDS-NOH (154 units), and MADDS (195 units). UVB-induced erythema was also significantly reduced in DDS-NOH– or MADDS-treated skin when compared with controls. Thus, these explorations show that dapsone metabolites exert pharmacodynamic effects when applied topically to the skin and may at least be equal to dapsone in their anti-inflammatory properties.[39,40]

In general, the UVB-suppressing activity of dapsone was subsequently confirmed by Schumacher,[41] who observed significant inhibitory capability of both topically applied (0,1%, 0,5%, 1%, 5%, 10%) and systemically applied dapsone (100 mg/d) on UV-induced erythema in healthy volunteers having sun-reactive skin type II and III (**Fig. 5**, **Table 1**). A theoretical explanation for the observed erythema-suppressing effect of dapsone could be the drug's inhibitory action on prostaglandins. Against this background, it is noteworthy that dapsone unexpectedly showed no substantial effect on anthralin-induced erythema, sodium dodecylsulfate–induced erythema, LTB_4-induced chemotaxis of PMN, and in psoriasis plaque test.[41,42]

However, the investigators did not con-

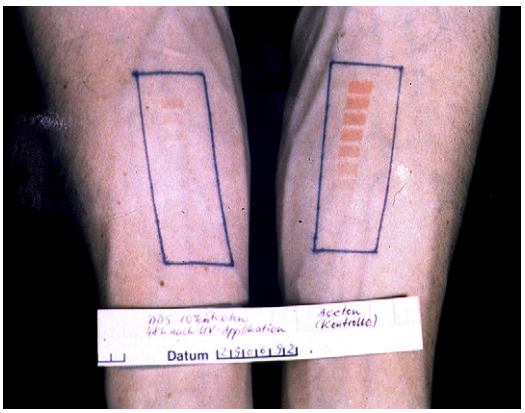


Fig. 5. Right forearm: suppression of ultraviolet (UV)-induced erythema with topically applied dapsone (1% solved in acetone, 48 hours after UV exposition). Left forearm: control.

DDS-NOH in the human models used. Regarding the effect of dapsone on chemotaxis, some controversial disparate results have been noted especially when comparing in vitro and in vivo studies. Some authors postulate even a selective inhibition of dapsone on specific chemotactic factors (eg, formyl-methionyl-leucyl-phenylalanine [fMLP]).[24,43]

Summarizing the mechanism of action of dapsone, a few theories have been postulated in an attempt to explain drug efficacy in chronic inflammatory disease states. However, little is known about the specific molecular effector systems targeted by dapsone or its metabolites, which leads to clinical efficacy. Further exploration of dapsone's mechanism of action in sulfone-sensitive dermatoses is needed.[44]

UNIQUE CHARACTERISTICS OF DAPSONE

Dapsone has unique pharmacologic properties among the spectra of available antiphlogistic agents. Currently, no other drug produces such a wide variety of beneficial activities:

1. Combination of antimicrobial and antiphlogistic effects (eg, treatment of opportunistic infections in patients with acquired immunodeficiency syndrome, use of dapsone in acne)
2. Safety of long-term treatment (eg, life-long use in leprosy, long-term ongoing or chronic intermittent approach in inflammatory dermatoses)
3. Disease-specific antiphlogistic activity (eg, prompt decrease of pruritus and control of skin lesions in dermatitis herpetiformis and amelioration of loxoscelism associated with brown recluse spider bites)
4. Steroid-sparing effect (eg, long-term treatment in autoimmune blistering diseases and as an adjuvant treatment in bronchial asthma)
5. UV protection (eg, suppression of UVB-induced erythema by dapsone and DDS-NOH)
6. Anticonvulsive effect (eg, in animal models)
7. Pharmacoeconomic benefits (eg, low cost of treatment).

CLINICAL USE OF DAPSONE

Dapsone, as a sulfone antibiotic, is used in rifampin-based multiple-drug regimens for treating multibacillary and paucibacillary leprosy.[10,13] Additionally, the sulfone alone or as part of drug combination with other antibiotic agents is used to treat prophylaxis of *P jiroveci* (*P carinii*) pneumonia and toxoplasmosis in individuals infected with HIV. The sulfone is designated an orphan

Table 1
Dapsone and erythema threshold

Application		Erythema Threshold Time (minimum)[a]		
Topical %	Systemic	Dapsone	Control	Difference
10	—	6.75 ± 1.27	4.14 ± 0.85	2.62 ± 0.74
5	—	5.79 ± 1.08	4.08 ± 0.74	1.72 ± 0.72
1	—	4.78 ± 0.82	3.38 ± 0.45	1.40 ± 0.55
0.5	—	4.97 ± 0.87	3.83 ± 0.51	1.14 ± 0.93
0.1	—	5.11 ± 1.07	4.22 ± 0.76	0.88 ± 0.46
—	100 mg/d	5.37 ± 1.19[b]	4.30 ± 1.06[b]	1.07 ± 0.34

[a] Dependent on the method of exposure in healthy volunteers (topical, n = 10; systemic, n = 8) with ultraviolet skin type II and III.
[b] Comparison between pre and posttreatment.

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