Dapsone and sulfones in dermatology: Overview and update

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In their 60-year history, dapsone and the sulfones have been used as both antibacterial and anti-inflammatory agents. Dapsone has been used successfully to treat a range of dermatologic disorders, most successfully those characterized by abnormal neutrophil and eosinophil accumulation. This article reviews and updates the chemistry, pharmacokinetics, clinical application, mechanism of action, adverse effects, and drug interactions of dapsone and the sulfones in dermatology. (J Am Acad Dermatol 2001;45:420-34.)

The father of sulfones is Emil Fromm, a professor in chemistry at the Freiburg/Br University in Germany. In 1908, Fromm and Wittmann[1] first described the synthesis of sulfones from *p*-nitrothiophenole. In vivo sulfone research was not initiated until 1937, when Buttle, Stephenson, and Smith[2] in England and Fourneau, Trefouel, and Nitti[3] in France treated experimental streptococcal infections in mice with dapsone and other sulfones, and Heitz, Nitti, and Trefouel[4] treated human gonorrhea with a disubstituted sulfone that had results comparable to those with sulfonamide. Dapsone derivatives rather than the parent compound were tested in humans initially, for fear of more severe side effects with dapsone.

Later in 1937, a sulfone derivative (sodium salt of p,p´-diaminodiphenyl-sulfone-N´-didextrose sulfate) was synthesized and put on the market under the name Promin by Parke, Davis & Co. This drug was investigated in the following years to treat various acid-fast bacilli infections. In 1940, Promin was used successfully by Cowdry and Ruangsiri[5] to treat *Mycobacterium leprae murium* infection in rats and by Feldman, Hinshaw, and Moses[6] to treat experimentally induced tuberculosis in guinea pigs.

The first clinical trial evaluating Promin in the treatment of leprosy was conducted in March 1941, and the result was published in 1943. Faget et al[7] reported that it inhibited the progress of leprosy in a considerable number of cases. The parent sulfone-dapsone was first used parenterally to treat human leprosy in 1945.[8] The first use of oral dapsone in leprosy was reported in 1949 by investigators in Brasilia, Nigeria, and the former French Guyana.[9]

Shortly thereafter, the use of sulfones in dermatology began. In 1950, Esteves and Brandao[10] reported their effectiveness in dermatitis herpetiformis. This was subsequently confirmed by other investigators.[11-16] The use of sulfones to treat subcorneal pustular dermatosis was first reported in 1956 by Sneddon and Wilkinson.[17] Sulfones are now generally accepted as the therapy of choice for this rare dermatosis. In the 1950s, investigators observed that patients with leprosy who also had acne vulgaris showed improvement of acne when treated with sulfones.[18] Since then, dapsone and sulfones have been used successfully to treat a broad range of dermatologic and systemic disorders.

Abbreviations used:

DH:	dermatitis herpetiformis
G6PD:	glucose 6-phosphate dehydrogenase
IgA:	immunoglobulin A
LTB_4:	leukotriene B_4
MPO:	myeloperoxidase
PCP:	*Pneumocystis carinii* pneumonia
PG:	pyoderma gangrenosum
RA:	rheumatoid arthritis
SWD:	Sneddon-Wilkinson disease
TMP-SMX:	trimethoprim-sulfamethoxazole
WHO:	World Health Organization

CHEMISTRY OF SULFONES

Dapsone (4-4´-diaminodiphenylsulfone, DDS) is structurally the simplest of the sulfones, all of which

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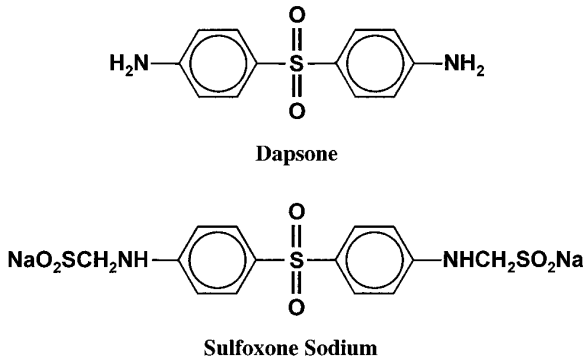

Fig 1. Structures of dapsone and sulfoxone sodium.

share the characteristic structure: a sulfur atom linking to two carbon atoms (Fig 1).

PHARMACOKINETICS

Absorption

Orally ingested dapsone is absorbed readily from the gastrointestinal tract with bioavailability of more than 86%.[19] Absorption is reduced in severe leprosy.[20] The disubstituted sulfones, such as sulfoxone, are poorly absorbed after oral administration, and large amounts are excreted in the feces.[21] In healthy volunteers, after 100 mg of oral dapsone, peak serum dapsone concentrations between 1.10 and 2.33 mg/L were reached within 0.5 to 4 hours.[22] The elimination half-life ranged from 12 to 30 hours.[22] Twenty-four hours after oral ingestion of 100 mg of dapsone, plasma concentrations ranged from 0.4 to 1.2 mg/L.[23] The therapeutic range of serum concentration is 0.5 to 5 mg/L for leprosy.[24] Serum levels stabilize after 8 to 10 days of therapy.[24] Dapsone pharmacokinetics in children are similar to those of adults, and dosing of children with 2 mg/kg daily or 4 mg/kg weekly results in peak concentrations equivalent to those reached in adults receiving 100 mg tablets daily.[25]

Distribution

Dapsone is approximately 70% protein-bound, and its monoacetylated metabolite is almost entirely protein-bound. Dapsone is distributed to all body organs including skin, liver, kidneys, and erythrocytes. Dapsone crosses the blood-brain barrier and the placenta and is found in breast milk.[20,21,26,27]

Metabolism

After absorption from the gastrointestinal tract, dapsone is transported through the portal circulation to the liver, where it is metabolized via acetylation or N-hydroxylation (Fig 2). N-hydroxylation yields the hydroxylamine, a potentially toxic metabolite produced by cytochrome P-450 enzymes, whereas acetylation by N-acetyltransferase yields the nontoxic metabolites monoacetyl dapsone and diacetyl dapsone.[24]

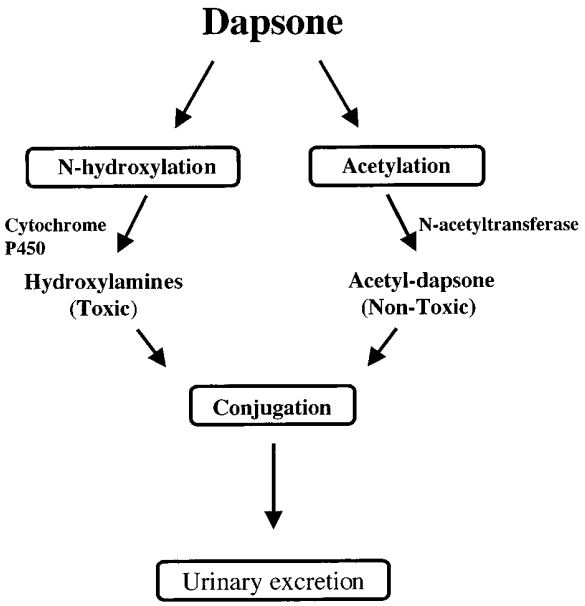

Fig 2. The two major metabolic pathways of orally ingested dapsone. After arriving in the liver via enterohepatic circulation, dapsone is metabolized by either N-hydroxylation to produce toxic hydroxylamines or by acetylation to produce nontoxic acetyl-dapsone. Acetyl-dapsone includes monoacetyl dapsone (MADDS) and biacetyl dapsone. Hydroxylamines include hydroxylated dapsone and hydroxylated MADDS. As in all biologic reactions, *arrows* should be viewed as reactions in equilibrium.

CYP3A was previously thought to be the major cytochrome isoform that hydroxylates dapsone, and the urinary recovery ratio of dapsone (amount of dapsone hydroxylamine excreted/amount of dapsone and its hydroxylamine excreted) was suggested as a putative in vivo CYP3A probe.[28] However, recent evidence indicates that more than one cytochrome P-450 enzyme is involved in dapsone hydroxylamine formation using human liver microsomes.[29,30] Studies with low molecular weight inhibitors illustrate the importance of CYP2E,[31] and CYP2C[32] in dapsone hydroxylation. Pretreatment with ketoconazole, an inhibitor of CYP3A, had no effect on dapsone hydroxylation in human subjects, indicating that CYP3A may not be significantly involved in dapsone N-hydroxylation in vivo.[33]

In a white population, dapsone N-hydroxylation exhibited a unimodal distribution with marked (tenfold) intersubject variability, and aging was associated with a reduced rate of hydroxylation.[34] Differential sensitivity of dapsone N-hydroxylation to selective CYP inhibitors indicated that the contribution of indi-

vidual CYP enzymes also varies between persons.[29] The levels of expression of these cytochrome P-450 enzymes may be an important determinant of individual susceptibility to the toxic effects of dapsone and may influence the ability of a specific enzyme inhibitor to block dapsone toxicity in vivo.

The acetylation ratio (monoacetyl dapsone:dapsone) measures the relative activity of each of these two metabolic pathways in an individual. It shows a genetically determined bimodal distribution and allows the definition of "slow" and "rapid" acetylators. Investigators have studied the effect of acetylation rate on the efficacy and toxicity of dapsone and suggest that the rate of acetylation does not affect the half-life[35] or the efficacy.[36] It remains controversial whether acetylation polymorphism affects dapsone toxicity. Although some investigators did not find a correlation between acetylation status and adverse effects,[36,37] others suggest otherwise.[38,39] Bluhm et al[39] measured the rate of acetylation and N-hydroxylation in patients treated with dapsone for inflammatory dermatoses and found that the 4 patients who experienced adverse effects were all slow acetylators and that 3 out of the 4 were fast hydroxylators. In patients with AIDS, slow acetylators have a higher incidence of adverse side effects than rapid acetylators.[38]

As dapsone goes through the enterohepatic circulation, its elimination half-life is markedly decreased after oral administration of activated charcoal. This permits successful treatment in some cases of toxicity.[40] Besides acetylation and hydroxylation, most dapsone and its derivatives are conjugated with glucuronic acid.[24]

Excretion

About 85% of dapsone is excreted in the urine, primarily as glucuronides; about 10% is excreted in the bile.[41] After a single dose of dapsone, about 50% is excreted during the first 24 hours.[42] Urinary excretion of dapsone can be decreased by administration of probenecid[43] and increased by rifampin.[44]

MECHANISMS OF ACTION OF DAPSONE

Antimicrobial action

As an antibiotic, dapsone acts in the same way as sulfonamides, inhibiting the synthesis of dihydrofolic acid through competition with *para*-aminobenzoate for the active site of dihydropteroate synthetase.[45] Therefore dapsone inhibits the growth of microorganisms that are dependent on endogenous folic acid synthesis.

Anti-inflammatory action

Dapsone is effective in dermatoses with abnormal neutrophil accumulation, through many potential mechanisms. Dapsone interferes with neutrophil chemotactic migration[46] and β2 integrin (CD11b/CD18)-mediated adherence of human neutrophils in vitro.[47] Dapsone interferes with the activation or function of the G-protein (Gi type) that initiates the signal transduction cascade common to chemotactic stimuli.[48] This inhibition suppresses neutrophil recruitment and local production of toxic respiratory and secretory products.[48]

Oxidants are important not only in the killing of bacteria, but they also participate in damaging bystander tissues in many disease processes.[49] Hypochlorous acid, the most important oxidant, is produced by the heme-containing enzyme myeloperoxidase (MPO) in neutrophils and by eosinophil peroxidase. In vitro studies have demonstrated that dapsone inhibits neutrophil MPO-mediated iodination and cytotoxicity at concentrations comparable to serum levels obtained by therapeutic doses.[50-52] Dapsone appears to bind to MPO, irreversibly converting it to an inactive compound (compound II), with chemical modification of the enzymatic active site.[53-55] Eosinophil peroxidase was found to be even more sensitive to inhibition by dapsone than MPO.[53] Thus dapsone appears to protect cells from neutrophil- and eosinophil-mediated injury by directly inhibiting the generation of toxic, oxygen-derived radicals.[56]

Systemic dapsone reduces leukotriene B_4 (LTB_4)-stimulated inflammation in mice, partly by inhibiting the binding of LTB_4 to specific receptors on neutrophils and by inhibiting neutrophil chemotactic response to LTB_4.[57] Dapsone inhibits the generation of 5-lipoxygenase products in human polymorphonuclear leukocytes and rat mast cells in vitro.[58,59] Dapsone also inhibits lysosomal enzymes.[60-62] Therefore, by multiple mechanisms, dapsone reduces the release of prostaglandins and leukotrienes and blocks their inflammatory effects.

Little is known about the mechanism of dapsone efficacy in antibody-mediated diseases such as linear immunoglobulin A bullous dermatosis (IgA dermatosis) and bullous pemphigoid. Thuong-Nguyen et al[63] evaluated the effect of dapsone on adherence of normal neutrophils to IgA and IgG from sera of patients with IgA dermatosis and bullous pemphigoid. Dapsone inhibits the adherence of neutrophils to basement membrane zone antibody in a dose-dependent manner. Serum from a patient taking dapsone inhibited neutrophil adherence, whereas the serum of the same patient when not receiving dapsone had no inhibitory effect. This experiment suggests a plausible mechanism for the clinical efficacy of dapsone, although more in vivo studies are needed.

Table I. Clinical indications of dapsone in dermatology (part 1)

Skin diseases	Regimen	Other therapy and comments
Acne fulminans	100 mg qd[204,205]	Case reports only[204,205]
Actinomycetoma	1.5-5 mg/kg qd for 1-2 y.[206] Most effective regimen is streptomycin with either dapsone or TMP-SMZ.[65]	In patients resistant to these treatments, adding amikacin cures about 95% of the cases. In true fungal mycetoma, treatment with amphotericin B, ketoconazole, itraconazole, and sometimes surgery is necessary.[206]
Brown recluse spider bites	100 mg qd[115]	Treatments include dapsone, systemic steroids, hyperbaric oxygen, antibiotics, and surgical excision.[78,79]
Cicatricial pemphigoid	150 mg qd required for acute episode control and 25-150 mg qd for maintenance[207]	Dapsone is the drug of choice.[208] Brief courses of prednisone and immunosuppressive agents such as azathioprine or cyclophosphamide in a daily dosage of 2-3 mg/kg are recommended to control individual episodes of severe recurrence.[209]
DH	25-100 mg qd alone or with gluten-free diet[14]	Dapsone has a 95%-97% response rate for DH[11] and remains the best tolerated therapy.[14]
Eosinophilic cellulitis	100 mg qd for treatment,[210] 50 mg qd with antihistamine and corticosteroid for maintenance.[211]	Other efficacious regimens include corticosteroid,[212,213] minocycline,[214] and antihistamine.[215,216]
Erythema elevatum diutinum	From 25-150 mg qd[217-219]	Case reports only.[217-219]
Granuloma annulare	100 mg qd for adults[220,221]	Spontaneous clearing is the rule but may take a long time. Resistant to many other therapeutic modalities.[222]
Granuloma faciale	200 mg qd for 6 wk-4 mo, 25-100 mg for maintenance[223-225]	No satisfactory treatment exists. Therapies investigated include electrodesiccation, surgical excision, intralesional corticosteroid injections, cryotherapy, dermabrasion, radiation therapy, gold injections, systemic corticosteroids, and antimalarial drugs.[224]

In summary, dapsone appears to predominantly affect the effector mechanisms, while having no influence on the initial pathogenic processes. This explains why dapsone is effective in treating a variety of dermatologic diseases that have different causes.

CLINICAL INDICATIONS

Dapsone is both an antibiotic and an anti-inflammatory agent. It is bacteriostatic against *Mycobacterium leprae* and is an essential component of leprosy treatment. It has also been used successfully to treat actinomycetoma,[64-66] in prophylaxis and treatment of *Pneumocystis carinii* pneumonia (PCP),[67-69] and for malaria.[70]

As an anti-inflammatory agent, dapsone has been used to treat many skin diseases characterized by the abnormal infiltration of neutrophils or eosinophils, such as erythema elevatum diutinum, dermatitis herpetiformis (DH), Sneddon-Wilkinson disease (subcorneal pustular dermatosis, SWD), linear IgA dermatosis, pustular psoriasis, pyoderma gangrenosum (PG), and Sweet's syndrome (Tables I and II). Among these, DH has the highest response rate (95%-97%).[11] Significant but lower response rates have been observed in erythema elevatum diutinum, linear IgA dermatosis, and SWD (see Tables I and II). Relapsing polychondritis has been successfully treated with dapsone and systemic corticosteroids[71-76] except for a few reported failures.[77] Most clinical indications of dapsone are based on anecdotal case reports, and there is a need for clinical trials to define its efficacy. Dapsone as an antineutrophilic agent has been effective in the treatment of brown recluse spider bites.[78,79]

Leprosy (Hansen's disease)

Despite progress in the management of leprosy over the past decades, the incidence of the disease has changed very little; 685,000 new cases were reg-

Table II. Clinical indications of dapsone in dermatology (part 2)

Skin diseases	Regimen	Other therapy and comments
IgA pemphigus	50 mg qd[132]	Dapsone is the first therapeutic choice. Etretinate, and systemic steroids are second-line therapies.[132]
Lichen planus	50-150 mg qd; for children 1-2 mg/kg qd[226]	Effective for erosive lichen planus[227,228]
Linear IgA dermatosis	50-450 mg qd[229]; for children, 1-2 mg/kg qd.[230,231]	No response to gluten-free diet.[232,233] Other treatments include sulfamethoxypyridazine[229] and colchicine.[234]
Pemphigus vulgaris	100 mg qd[120]	Dapsone is an adjuvant therapy to corticosteroid.[121]
PP	1 mg/kg qd combined with tripterlide and erythromycin[235]	Short-contact anthralin therapy and topical PUVA for localized PP. Clofazimine,[105] methotrexate, hydroxyurea, etretinate, cyclosporin, and systemic corticosteroids may be used for generalized PP.[236]
Pyoderma gangrenosum	100-300 mg qd alone or combined with corticosteroid[109-111]	No single regimen is effective for all patients.
Relapsing polychondritis	100-200 mg qd for 3-4 mo, then taper to maintenance dose[72,73]	Dapsone and/or systemic corticosteroids are the most effective therapies.[76,237]
Sneddon-Wilkinson disease	50-150 mg qd[17,238]	
Sweet's syndrome	100-200 mg qd[239]	Systemic steroid is first-line therapy[240,241]; dapsone was recommended as first-line therapy for recurrent neutrophilic dermatosis of the dorsal hands.[242]

PP, Pustular psoriasis.

istered in 1997.[80] With international travel, leprosy may be found anywhere.

Treatment of leprosy is generally guided by the recommendations of the World Health Organization (WHO). For paucibacillary patients, they recommend 600 mg of rifampicin monthly, supervised, and 100 mg of dapsone daily, unsupervised, for 6 months before therapy can be discontinued.[81] For single-lesion paucibacillary leprosy, the 7th WHO Expert Committee on Leprosy recommends a single dose of 600 mg rifampicin, 400 mg ofloxacin, and 100 mg minocycline, based on a multicenter trial.[82,83] For multibacillary cases, WHO recommends 600 mg of rifampicin and 300 mg of clofazimine monthly, supervised, and 100 mg of dapsone and 50 mg of clofazimine daily, unsupervised for 12 months.[83,84]

Pneumocystis carinii pneumonia

The treatment of choice for PCP remains trimethoprim-sulfamethoxazole (TMP-SMX).[67,68] Those with mild to moderate disease may receive dapsone-trimethoprim or clindamycin-primaquine if TMP-SMX is contraindicated.[67,68] However, both dapsone-trimethoprim and clindamycin-primaquine regimens are contraindicated in glucose 6-phosphate dehydrogenase (G6PD) deficiency.[67,68] For this purpose, atovaquone should be used in patients who are deficient in G6PD and unable to take either TMP/SMX or pentamidine.[85]

Dapsone is an alternative drug for PCP prophylaxis in both adults and children intolerant to TMP-SMX and pentamidine.[69,86-92] However, dapsone is probably not as effective as TMP-SMX in preventing PCP. Retrospective cohort studies showed that dapsone prophylaxis is associated with significantly higher rates of PCP than TMP-SMZ after allogeneic marrow transplantation.[93-95] Therefore dapsone should be used as only a second or third choice for PCP prophylaxis.

Dermatitis herpetiformis

DH is a lifelong, blistering skin disease with pathognomonic IgA deposits in the papillary dermis.[96,97] Both the histopathologic and skin abnormalities in DH respond to gluten-free diet.[98,99] In 1950 the first report of successful use of dapsone in the treatment of DH was published.[10] Since then, clinical studies and many case reports have established dapsone as the best tolerated pharmacologic therapy for DH in both adults and children.[11-16] If patients constantly adhere to the gluten-free diet, the dosage of dapsone required to suppress the skin

lesions can be gradually reduced and eventually discontinued in most patients.[98,99]

Pyoderma gangrenosum

PG, an ulcerative skin disease of unknown origin, is associated with many systemic diseases including inflammatory bowel disease and rheumatoid arthritis (RA).[100,101] PG is challenging to treat, and no single regimen is effective for all patients. Effective pharmacotherapy may include prednisone (intralesional and oral),[102] sulfonamides,[101] cyclosporine,[103,104] clofazimine,[105] thalidomide,[106] methotrexate,[107] and intravenous human immunoglobulin.[108] Dapsone alone or in combination with prednisone has been used successfully to treat PG.[109-111]

Brown recluse spider

The venom of the brown recluse spider may cause severe necrosis and hemolysis.[112-114] Local envenomation begins with pain and itching, progressing to vesiculation with violaceous necrosis, extensive surrounding erythema, and ulceration.[115] These ulcers may require complex surgical reconstruction with flaps or grafts. In the worst scenario, *Loxosceles* envenomation has caused renal failure, seizures, and even death. Dapsone, 100 mg/day, has emerged as a promising pharmacotherapeutic agent in both animal studies and human clinical trials for systemic envenomation.[115-117] In two retrospective studies of 31 patients each, pretreatment with dapsone not only reduced surgical complications but also improved the outcome of patients.[78,79]

Pemphigus vulgaris

In 1976, Rosenberg, Sanders, and Nelson[118] reviewed 107 consecutive cases of pemphigus, finding dapsone a useful adjuvant to systemic corticosteroids. Its usefulness as a steroid-sparing agent has been supported by other investigators.[119-123] Dapsone is occasionally effective if used alone in uncomplicated cases of pemphigus.[124,125]

IgA pemphigus

IgA pemphigus covers a broad spectrum of diseases characterized by vesiculobullous or vesiculopustular lesions with intercellular IgA deposition, first described in 1979.[126] Other names that have been used for IgA pemphigus include intraepidermal neutrophilic IgA dermatosis,[127] IgA pemphigus foliaceus,[128] IgA herpetiform pemphigus,[129] intraepidermal IgA pustulosis,[130] and intercellular IgA vesiculopustular dermatosis.[131] There are two subtypes of IgA pemphigus, one is the subcorneal pustular dermatosis type resembling SWD, and the other is the intraepidermal neutrophilic IgA dermatosis type.[132] Despite the difference in clinical, histologic, and immunologic characteristics between these two subtypes, dapsone is the first choice regimen for both of them.[129,132-134]

Table III. Baseline monitoring guidelines

Clinical evaluation	Careful history and physical examination to identify patients at increased risk for toxicity
Laboratory evaluation	CBC with differential WBC count and reticulocyte count
	Serum chemistry including liver function test and renal function tests
	Urinalysis
	G6PD level

CBC, Complete blood cell count; *WBC,* white blood cell.

Rheumatoid arthritis

For noncutaneous inflammatory diseases including RA, dapsone has shown efficacy in randomized clinical trials and individual case reports.[135-140] Dapsone is superior to placebo and comparable to chloroquine and hydroxychloroquine; it is considered an effective second-line agent in the treatment of RA.[135]

ADVERSE EFFECTS

Overall, the risk of dapsone-dependent side effects is very low if the plasma concentration is below 5 mg/L.[24] Although the therapeutic range for leprosy was estimated to be 0.5 to 5 mg/L, the ranges for other indications are not known. Metabolism of dapsone by cytochrome P-450 to hydroxylamines is responsible for some dapsone side effects including methemoglobinemia, hemolysis, and fatal agranulocytosis, but the mechanism by which hydroxylamines cause these side effects is unclear (Table III).

Methemoglobinemia

Methemoglobinemia is the most common side effect of dapsone. The methemoglobinemia caused by dapsone is normally well tolerated at low to moderate dapsone doses, but may become a serious problem at dosages exceeding 200 mg/d.[45] Hydroxylamine metabolites react with hemoglobin, in the presence of oxygen, leading to methemoglobin formation. When nicotinamide adenine dinucleotide phosphate is available, hydroxylamine metabolites can be regenerated, leading to more methemoglobin formation.[24] Under normal conditions, methemoglobin is reduced by nicotinamide adenine dinucleotide–dependent methemoglobin reductase. Persons with a deficiency of this nicotinamide adenine dinucleotide–dependent

enzyme or with a hemoglobinopathy are more susceptible to methemoglobinemia.[141]

Hemolysis

Hemolysis with Heinz-body formation and frank anemia from dapsone therapy have long been recognized. The average hemoglobin in leprosy patients treated with daily dapsone falls significantly by almost 2 g/dL before reaching a nadir, whereas in 16% of patients the hemoglobin falls at least 3 g/dL.[142] Increasing age and daily dose have been associated with an increased magnitude of dapsone-related hemolysis.[142] In vitro and in vivo studies have demonstrated a direct involvement of hydroxylamines in hemolysis.[143-145] Exposure of rat red blood cells to hydroxylamine metabolites in vitro with subsequent readministration to isologous rats results in premature splenic sequestration of the damaged cells.[143,145] The exact mechanism of hemolysis is not known, and it is hypothesized that oxygen free radicals are involved.[146] To minimize hemolysis, daily dapsone dosage should not exceed 1.5 mg/kg body weight or 100 mg in normal healthy persons, and 50 mg in healthy G6PD-deficient persons.[147]

G6PD deficiency and dapsone side effects

G6PD-deficient patients are less susceptible to methemoglobinemia and more susceptible to hemolysis. G6PD deficiency leads to the impairment of the hexose monophosphate shunt, and thus to a decrease in NADPH formation. Consequently, the regeneration of hydroxylamine metabolites of dapsone and their effect on methemoglobin formation are reduced.

Persons deficient in erythrocytic G6PD show about a 2-fold increase in sensitivity toward dapsone-induced hemolytic anemia. Treatment of red blood cells with epiandrosterone, a potent inhibitor of rat red blood cell G6PD and hexose monophosphate shunt, resulted in about a 2-fold increase in sensitivity of the rat cells to N-hydroxydapsone hemolytic activity, and a modest but significant increase in depletion of red blood cell glutathione.[143,144] However, treatment of leprosy for G6PD-deficient patients on 600 mg dapsone per week for a long period of time did not lead to significant hemolysis.[148]

Agranulocytosis

The mechanism of dapsone-induced agranulocytosis is unclear but may involve erythrocytes.[149] Erythrocytes exposed to hydroxylamine and repeatedly washed may still release this metabolite in sufficient concentration to kill mononuclear leukocytes in vitro.[149] Thus erythrocytes may be a conduit for hydroxylamine to reach the bone marrow, where it can covalently bind to granulocyte precursors, triggering an immune response in certain persons and leading to the potentially fatal agranulocytosis.

Other rare side effects with unknown mechanism

The spectrum of dapsone side effects seems to be as broad as its clinical indications; fortunately, however, most are rare. One such side effect of dapsone is the "dapsone syndrome," a hypersensitivity reaction presenting with the triad of fever, rash, and internal organ involvement. Cutaneous lesions include erythematous papules, plaques, pustules, and eczematous lesions.[150,151] Only a few cases have been reported in patients taking doses of less than 100 mg/d, and the incidence was estimated to be less than 0.5%.[152,153] Other manifestations of this syndrome include pruritus, lymphadenopathy, jaundice with hepatic dysfunction, mononucleosis, eosinophilia, photosensitivity, hepatomegaly, and splenomegaly.[135,150,152-154] The interval between drug initiation and hypersensitivity reaction varies from case to case. Some authors suggest that the reaction happens within 1 to 6 weeks,[155,156] whereas others suggest anytime after 4 weeks.[151] On average, this syndrome occurs 27 days after the initial ingestion of dapsone.[150] Elevated erythrocyte sedimentation rate and liver enzyme levels were invariable findings in the "dapsone syndrome."[150]

Other medications that may cause similar hypersensitivity syndromes include antiepileptics,[157] sulfonamide antibiotics such as sulfamethoxazole,[158] allopurinol,[159,160] nonsteroidal anti-inflammatory drugs,[161] minocycline,[162,163] terbinafine,[164] and azathioprine.[165,166] In some patients, hypothyroidism may occur 3 months or more after onset of the hypersensitivity reaction.[167]

In isolation or as part of the dapsone syndrome, other side effects associated with dapsone include neurotoxicity (minor neurologic complaints to peripheral neuropathy[168-170] and psychosis[171-173]), hepatotoxicity (toxic hepatitis),[174,175] renal toxicity (nephrotic syndrome and renal papillary necrosis),[176,177] and minor gastrointestinal complaints.[178] Neurotoxic reaction is considered idiosyncratic and dose-independent,[168,171] even though it was never observed in many patients on a dosage of 25 mg/d.[179] A case of Stevens-Johnson syndrome was reported to be likely induced by administration of dapsone.[180]

Monitoring and prevention of dapsone side effects

The clinician should avoid concomitant therapy with drugs associated with hemolysis or blood

Table IV. Major adverse effects of dapsone

	Incidence rate and relation to dosage	Follow-up monitoring guideline[243]
Hemolysis	80% patients reduced Hb by 1 g/dL, and 10% reduced Hb by 2 g/dL at 100-150 mg qd[244,245]	Especially in G6PD-deficient patients; CBC count with differential WBC count and reticulocyte count every 2 wk for first 3 mo, then every 3 mo
Methemoglobinemia	At >200 mg qd, methemoglobin can reach 10% of total Hb	Monitor methemoglobin levels in patients with cardiopulmonary disease, hemoglobinopathy, or methemoglobin reductase deficiency
Agranulocytosis	1 in 240 to 425 idiosyncratic and dose independent[246]	Monitor CBC count 4-10 wk after initiation of therapy; stop therapy when WBC count <4000/mm^3
Peripheral neuropathy (primarily motor but can also include sensory deficit)	Rare, typically occurs at >300 mg qd, complete recovery after dose reduction or withdrawal,[167-169] may occur at 100 mg qd[247]	Periodic neurologic screening examination by dermatologist; any suspected abnormality needs referral for full neurologic examination and electromyogram with nerve conduction studies
Psychosis	Rare, if dosage is <100 mg qd[172]	Manifested by insomnia, irritation, excitability, and even violence; reversible on stopping dapsone[170]

CBC count, Complete blood cell count; *Hb,* hemoglobin; *WBC count,* white blood cell count.

dyscrasias, such as sulfonamides, isoniazid, aspirin, ibuprofen, and primaquine, especially in G6PD-deficient patients. As discussed previously, whether acetylation polymorphism affects the risk of experiencing hematologic side effects is still disputed. Guidelines for monitoring the side effects of dapsone are presented in Tables III and IV. Unfortunately, there is no reliable way to predict the risk of dapsone hypersensitivity. Successful treatment of the dapsone syndrome with 30 to 60 mg/d of oral prednisolone has been reported.[153,168]

HOW TO INCREASE TOLERANCE TO DAPSONE

Use of a metabolic inhibitor such as cimetidine to reduce hepatic oxidation of dapsone to hydroxylamine has successfully decreased its adverse effects.[181] Methemoglobin formation in the presence of cimetidine was maintained at 30% below control levels for almost 3 months, and the incidence of reported side effects such as headache and lethargy were significantly reduced.[182] Long-term concurrent cimetidine administration increased plasma dapsone levels without increased hemolysis and reduced methemoglobinemia for more than 2 months.[183] The concomitant use of cimetidine is recommended to increase patient compliance, especially in patients receiving dapsone dosages in excess of 200 mg/d.[149] Because of the previously mentioned interindividual variation of hydroxylation enzymes and the involvement of more than one cytochrome isoform in dapsone hydroxylation, selective cytochrome inhibitors cannot produce complete inhibition of hydroxylation and are unlikely to offer any clinical advantage over cimetidine in decreasing dapsone toxicity in vivo.[29]

Because oxygen radicals are thought to be involved in dapsone-induced hemolytic anemia,[146] antioxidants such as vitamins C and E may be protective against this adverse effect. In 1984, Kelly et al[184] reported that in patients receiving dapsone at 100 mg/d, vitamin E therapy at 800 mg/d up to 3 months does not substantially ameliorate the hemolytic effect of this drug. However, a more recent clinical study found that oral administration of 800 U of vitamin E daily for 4 weeks conferred partial protective effect against dapsone-induced hemolysis in patients with DH. Vitamin C was not found to be effective in this study.[185] Both these studies have limitations because they were not randomized, placebo-controlled, and blinded clinical trials. More studies are warranted to clarify the usefulness of vitamin E in reducing side effects of dapsone.

USE DURING PREGNANCY AND LACTATION

Pregnancy may be a trigger of leprosy and other dermatologic diseases because of the changes in cell-mediated and humoral immunity during gestation.[186,187] First appearance of leprosy, reactivation of the disease, and relapse in "cured" patients are likely to occur particularly in the third trimester of pregnancy.[188] Because up to 20% of children born to mothers with leprosy may experience leprosy by puberty,[188] pregnant women with leprosy require treatment.

Table V. Drugs affecting dapsone and other sulfones

Names of drugs	Effects on dapsone
Trimethoprim	Increases plasma concentration and adverse effects of dapsone[248]
Rifampin	Induces dapsone metabolism by causing a proliferation of the smooth endoplasmic reticulum and an increase of cytochrome P-450 content in the liver[249]; also enhances urinary excretion of dapsone[250]
Pyrimethamine (together with dapsone as Maloprim)	Increases the volume of distribution and lowers the peak serum concentration of dapsone[251]
Probenecid	Reduces urinary excretion of dapsone with an increase in plasma concentration of dapsone[43]
Cimetidine	Inhibits formation of the toxic hydroxylamine metabolite of dapsone and increases the therapeutic/toxic ratio[183]
Omeprazole	Inhibits cytochrome enzymes and decreases the rate of hydroxylamine formation[252] in white subjects but not in Chinese subjects[252]

Treatment with dapsone for various diseases during pregnancy is generally considered to be safe for both mother and fetus.[189-192] There have been a few case reports of neonatal complications after maternal dapsone therapy, including neonatal hemolytic disease,[193] neonatal hyperbilirubinemia,[194] and neonatal methemoglobinemia.[195] Dapsone can cross the placenta[24] and is found in limited amounts in breast milk.[27]

DRUG INTERACTIONS

Drugs that affect the pharmacokinetics and efficacy of dapsone are listed in Table V. Concurrent administration of clofazimine in combination therapy of leprosy does not appear to affect the excretion of dapsone.[196]

Concurrent administration of other substrates of the same enzymes that metabolize dapsone may influence the efficacy and toxicity of dapsone. For instance, dapsone, isoniazid, and sulfamethazine are probably acetylated by the same N-acetyltransferase, and when either is administered with dapsone to healthy human subjects, the acetylation rate of dapsone was decreased.[197] This drug interaction could potentially increase the toxicity of dapsone. However, no clinical relevance of this interaction has been reported.

Other drugs may also influence dapsone metabolism through their influences on cytochrome P-450. Inducers of cytochrome P-450 such as glucocorticoids and anticonvulsants may potentially increase N-hydroxylation of dapsone to hydroxylamine.[198] Coadministration of other drugs such as macrolide antibiotics and azole antifungals that are inhibitors of cytochrome P-450 potentially decreases the rate of dapsone hydroxylation and its toxicity, if dapsone has lower affinity for the enzyme.[199] Within the class of macrolides, erythromycin has the greatest inhibition of CYP3A followed by clarithromycin, whereas azithromycin has no effect at all.[200,201] Among azole antifungal medications, ketoconazole is a more effective inhibitor of CYP3A than itraconazole, which is more effective than fluconazole.[202,203] One may infer that fluconazole will have the least interaction of any azole antifungal, and azithromycin will be the safest macrolide for concomitant use with dapsone.

Because more than one cytochrome P-450 isoform is involved in the hydroxylation of dapsone, other drugs can interact with dapsone through different isoforms, including CYP3A, CYP2C, and CYP2E (see "Metabolism"). Because the relative contributions of these isozymes probably have significant interindividual variability, the clinical significance of the selective inhibitors of cytochrome isoforms on dapsone is undefined, and more clinical data are needed to clarify this issue.

Despite major advances in pharmacotherapy of dermatologic disorders in the past several decades, dapsone retains its niche in the dermatologist's therapeutic armamentarium.

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