

Review Article

Dapsone: use in immunobullous dermatoses

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Abstract Dapsone and other sulfonamides have been used successfully in the treatment of patients with a variety of blistering skin diseases. The patients most likely to respond to dapsone therapy have predominantly neutrophilic infiltrate in their skin e.g. dermatitis herpetiformis and linear IgA disease. The precise mechanism of action of dapsone is unknown. *In vitro* studies have shown that dapsone can interfere with the production of and response to neutrophilic chemotactants and that it may impair the neutrophils' ability to localize to sites of inflammation and produce toxic oxygen intermediates. The safe use of dapsone requires an understanding of the pharmacology and adverse effects of the drug. Hemolytic anemia and methemoglobinemia are two of the dose-related adverse effects. Agranulocytosis, motor neuropathy, and dapsone hypersensitivity syndrome are some of the severe idiosyncratic effects that can occur in patients treated with dapsone. Careful patient selection and close monitoring of patients during therapy with dapsone are critical elements in the safe and effective use of dapsone for patients with blistering skin diseases.

Key words

Dapsone, toxicity, dermatitis herpetiformis, linear IgA disease, bullous pemphigoid, cicatricial pemphigoid, bullous SLE, epidermolysis bullosa acquisita, pemphigus.

Introduction

During last 60 years, dapsone and the other sulfones have been used as both antibacterial and anti-inflammatory agents. Dapsone has been used successfully to treat a wide range of dermatologic disorders especially those characterized by abnormal neutrophilic and eosinophilic accumulation.

In 1940, Costello first described the success of sulfapyridine in treating dermatitis herpetiformis (DH).¹ Swartz and Lever² later affirmed this therapeutic response of DH to sulfapyridine. In the early 1950s, sulfones

(dapsone and related compounds) were first used in treating patient with this disease.²

Pharmacology***Absorption and bioavailability***

Dapsone is a lipid-soluble compound that penetrates well into cells and tissues. It is well absorbed from the gut with approximately 70-80% of a single oral dose absorbed. Its absorption half-life is about 1 hour.^{3,4} Dapsone's greater efficacy than other sulfonamides is probably related to its superior absorption from the gut and its effective penetration into the cell. The absorption is not impaired in DH with or without symptomatic intestinal involvement.^{5,6} Dapsone crosses the placenta and is excreted in the breast milk and hemolysis has been reported in nursing

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infants of mothers taking dapsone.⁷ However, it is not teratogenic.⁸ A steady state of a mean concentration of 1.82-1.95 mg/l is achieved in 6-28 days of 100mg/day therapy. The elimination half-life averages between 24 and 30 hours, with significant individual variability ranging from 14 to 83 hours. This long elimination half-life is secondary to significant enterohepatic recirculation of the drug and the strong protein binding of dapsone (70-90%) and its major metabolite, monoacetyl dapsone (99%). Dapsone remains in the circulation for as long as 35 days.⁹

Metabolism

Dapsone is primarily metabolized by N-acetylation and N-hydroxylation. There is significant variability in acetylation, with some individuals being "rapid acetylators." The second major mechanism of dapsone metabolism is hydroxylation. N-hydroxylation of dapsone occurs in the liver, mediated by various cytochrome P-450 enzymes, including CYP2E1, CYP2C9, and CYP3A4.¹⁰ This hydroxylamine metabolite is considered to cause the dapsone-induced hematologic adverse effects i.e. methemoglobinemia and hemolytic anemia.^{11,12} This hydroxylation can be inhibited *in vivo* by cimetidine, which blocks several cytochrome P-450 enzymes.

Excretion

Dapsone and its metabolites are conjugated in the liver to glucuronides, which are water soluble and rapidly excreted by the kidneys. Treatment with probenecid decreases renal clearance of dapsone whereas activated charcoal interrupts dapsone's enterohepatic circulation and increases the rate of elimination up to five times,⁹ making it

useful in cases of acute toxicity or overdose of dapsone. In liver diseases there is minor change in the metabolism of dapsone, and no dose adjustment appears to be needed. The use of dapsone in renal failure has not been thoroughly investigated.¹³

Mechanisms of action

While dapsone's mechanism of action in the treatment of leprosy has been shown to be due to its inhibition of the folic acid pathway, its mechanisms in inflammatory diseases e.g. immunobullous disorders are not well understood. It has also been suggested that dapsone may inhibit the ability of neutrophils to function at the sites of inflammation.⁴

Impairs neutrophils chemotaxis

Dapsone affects neutrophil chemotaxis in multiple ways. It has been shown to block the production of and neutrophil response to chemotactants. To generate an inflammatory response, chemotactants must first be produced. It has been demonstrated that dapsone inhibits the release of IL-8, a known neutrophil chemotactic agent, from keratinocytes exposed to one of the pathogenic autoantibodies in bullous pemphigoid.¹⁴ Dapsone also inhibits leukotriene B4 production, LTB4-neutrophil interactions and neutrophil chemotaxis to LTB4.^{15,16}

After neutrophils have sensed the inflammatory signal, they must be able to localize to the area of inflammation and migrate through the tissues. Dapsone inhibits the migration and adherence of neutrophils to IgA or IgG-coated normal epidermal basement membrane. It affects

integrin-mediated neutrophil adherence to endothelium, a necessary step prior to diapedesis of those cells into inflamed tissue.

Impairs neutrophil function

Dapsone has been demonstrated *in vitro* to impair the function of neutrophil myeloperoxidase and other lysosomal enzymes and thus the production of toxic oxygen intermediates.^{17,18} It is demonstrated that dapsone inhibits the myeloperoxidase halide-mediated cytotoxic system; therefore modulating the degree of tissue destruction in lesions.¹⁷ This effect preferentially occurs at a higher pH.¹⁹

Clinical use

Besides DH and leprosy, dapsone has shown activity in a variety of skin diseases. Dapsone-responsive immunobullous dermatoses can be divided into two general categories: those in which the response has been clearly documented and those in which the response has been noted only anecdotally or in a minority of treated patients. In case of dapsone-responsive dermatosis, the patient experiences a relatively rapid response (within 24-48 hours), with a similar rapid recurrence of symptoms

Immunobullous disorders showing consistent efficacy

Dermatitis herpetiformis (DH) Dapsone is the drug of choice for the treatment of DH. The majority of patients can be controlled with 100-200 mg/day of dapsone. An incomplete response should prompt a dose escalation; a few patients require as much as 400 mg/day of dapsone. However, in view

of dose-related adverse effects, self-medication and self-adjustment of the dapsone dose by the patients should be discouraged. Similarly, patients must be evaluated before starting therapy for any factors that may increase the toxicity of drug.^{20, 21}

Linear IgA bullous dermatosis (LABD) and chronic bullous dermatosis of childhood (CBDC) Most of the patients with LABD can be controlled with 100-200 mg/day of dapsone. In both DH and LABD, maintenance therapy is usually required for some period before withdrawal is successful, a dose of 50 mg every other day has been suggested as an average maintenance dose.^{22, 23}

Bullous eruption of systemic lupus erythematosus Patients with the bullous eruption of systemic lupus erythematosus (SLE) have a vesicular eruption with histology similar to that seen in patients with DH. The blistering only sometimes parallels the other signs and symptoms of SLE. The bullous eruption, however, responds dramatically to dapsone therapy in doses as low as 50 mg/day. Since other systemic manifestations of SLE can potentiate the clinical severity of the effects of dapsone e.g. anemia, these patients should be monitored more carefully both before and during therapy.²⁴

Immunobullous dermatoses with variable efficacy

A wide variety of other diseases have shown variable responsiveness to dapsone therapy. Dapsone has been reported to be of some use in the treatment of bullous pemphigoid, cicatricial pemphigoid, IgA pemphigus (subcorneal pustular dermatosis-like

variety), pemphigus vulgaris, pemphigus foliaceus, and epidermolysis bullosa acquisita (EBA).²⁴ Dapsone has also been a useful adjunct in inflammatory diseases of the skin for which systemic corticosteroids are the treatment of choice.²⁴⁻²⁹

Bullous pemphigoid (BP) Dapsone has been used in BP with variable response ranging from about 10% to 60%. Patients with BP, especially those with a predominantly neutrophilic infiltrate respond better.²⁹

Cicatricial pemphigoid (CP) CP is associated with different immunologic findings which may mimic LABD, BP, EBA, or others. Although no prospective, controlled studies have been done, most studies suggest that dapsone is an effective drug for patients with CP, especially in those with predominantly oral or ocular disease.

Epidermolysis bullosa acquisita (EBA) Little data exist about the efficacy of dapsone in EBA. The lack of a predominantly neutrophilic infiltrate in most patients with EBA suggests that dapsone may not be an effective drug.

Pemphigus Use of dapsone as the initial treatment in superficial pemphigus i.e. pemphigus foliaceus, and pemphigus erythematosus has been documented.³⁰ Dapsone has also been used in patients with subcorneal pustular dermatosis-like IgA pemphigus.^{31,32} Dapsone has proven to be effective in these patients, although some also required systemic corticosteroids to achieve full remission. In addition, dapsone has been used in the treatment of patients with pemphigus vulgaris, most often after they have failed prednisone.²⁷ Dapsone may

be useful as a steroid-sparing agent in these patients.

Contraindications

Dapsone is contraindicated in patients with documented hypersensitivity drug. A relative contraindication to the use of dapsone is dose-related, pharmacological adverse events. Patients with increased risk for these events due to cardiopulmonary or hematological disease or glucose-6-phosphate dehydrogenase (G6PD) deficiency should be monitored with great care.

Adverse effects

Pharmacologic

Hemolytic anemia Methemoglobinemia and hemolytic anemia are well-recognized adverse events associated with dapsone and occur to some degree in all individuals taking the drug. This hematological toxicity is due its N-hydroxy metabolites.^{11,12,33} These metabolites are-potent oxidants. The ability of erythrocytes to tolerate oxidative stress is related to their supply of reduced glutathione and the ability of the hexose monophosphate shunt to repair oxidative damage. Since red blood cells cannot synthesize new proteins, the ability of the red blood cells to resist oxidative stress decreases with time. Oxidative damage causes structural changes to the red cell membrane. Such cells are then removed by the circulation by the spleen (extravascular hemolysis).¹¹ Increased susceptibility to hematological adverse effects is seen in individuals deficient in G6PD. G6PD deficiency results in impairment of the hexose monophosphate

shunt and a diminished supply of glutathione.³⁴

Methemoglobinemia Methemoglobin is formed when the iron within the heme molecule is oxidized to the ferric state by the hydroxylamine metabolite of dapsone. There is no clear relationship between the hemolytic anemia and methemoglobinemia seen in patients taking dapsone. Methemoglobin cannot carry oxygen. It can reduce overall oxygen delivery only at concentrations greater than 30% in normal individuals. Symptoms and signs of toxicity include lethargy, headache, dyspnea, and cyanosis.³⁵ It is not possible to predict the degree of methemoglobinemia based on the degree of cyanosis of the patients.

Vitamin E (800 IU/day) has been demonstrated to improve subclinical markers of hemolysis and lower methemoglobin levels in patients taking dapsone; however, clinical benefits have not been documented.³⁶ Cimetidine temporarily decreases methemoglobin formation in patients being treated with dapsone.³⁷ The methemoglobin levels returned to baseline after 2 months of therapy, despite continued use of cimetidine.³⁸ In severe methemoglobinemia, oral (100-300 mg/day) or intravenous methylene blue (1 mg/kg over 5 minutes with a repeated dose in 30-60 minutes) can be used to acutely decrease methemoglobin levels.³⁹

Idiosyncratic

Agranulocytosis Agranulocytosis is one of the most serious idiosyncratic reactions to dapsone.^{39,40} The exact mechanism of the agranulocytosis is not known, however, several hypotheses have been proposed. It is

known that the hydroxylamine metabolite of dapsone is scavenged by erythrocytes and that this cytotoxic metabolite might be delivered to the bone marrow in erythrocytes, where it leeches out and damages neutrophil precursors. Another hypothesis is that the myeloperoxidase within the neutrophil precursors in the bone marrow produces the hydroxylamine metabolite locally. However, dapsone interferes with the function of myeloperoxidase and so it is unlikely that this mechanism could produce significant toxicity to the bone marrow.⁴¹ Dapsone, by inhibiting G-proteins, might block a highly specific mechanism of cell control rather than act as a direct toxin or produce a hapten-mediated immune response.

Neuropathy Dapsone has been associated with several adverse neurologic events. The most common, although still rare, is a peripheral neuropathy.⁴²⁻⁴⁶ This neuropathy primarily involves the distal motor nerves, with evidence of axonal degeneration by electrophysiology. Although a sensory component has been seen in a minority of patients, it has always been associated with motor findings.⁴⁶ Patients most typically present with weakness of their hands and/ or legs, often with wasting of their hand muscles. Usually patients do not have other signs of severe dapsone toxicity (sulfone syndrome, severe anemia, methemoglobinemia). The dose of dapsone associated with the development of neuropathy ranges from 75 to 600 mg/day, although most cases have been reported in patients taking more than 300 mg/ day. Most patients recover completely with discontinuation of the drug, although recovery may be delayed or incomplete.⁴⁵

For patients who cannot tolerate being off dapsone, a decrease in the dose, a temporary drug holiday is recommended to prevent this drastic adverse effect.

Other neurologic effects Permanent optic nerve atrophy,⁴⁷ acute psychosis,⁴⁸⁻⁵⁰ headache and nervousness³⁸ have been reported in patients taking dapsone.

Gastrointestinal effects A variety of gastrointestinal adverse events have been associated with dapsone. Some patients experience mild gastrointestinal upset that is usually self-limited and can be controlled by taking the drug with meals. Patients on dapsone have been reported to develop primary hepatocellular hepatitis as well as cholestatic hepatitis; both resolve with discontinuation of the drug in 10-14 days.^{51,52} It is noted that elevated transaminases were associated with blood sulfone levels greater than 2 mg/dl, suggesting a direct hepatotoxic effect.⁵² Other rare gastrointestinal adverse events associated with dapsone include severe hypoalbuminemia (thought secondary to an autoimmune reaction to albumin) and pancreatitis.⁵³

Dapsone hypersensitivity syndrome A more severe adverse event associated with dapsone has been called the "dapsone syndrome" or "sulfone syndrome." It is an idiosyncratic, dose independent, multiorgan disease that, unlike many drug reactions, can begin after prolonged exposure to the drug. This syndrome usually appears after more than 4 weeks of therapy and occurs in less than 0.5% of treated patients.⁵⁴ The hydroxylamine metabolite has been postulated to be involved in the pathogenesis of this syndrome, perhaps acting as a

chemical antigen in an autoimmune reaction. Older age and preexisting liver disease are thought to be somewhat protective, as the activity of the hepatic enzyme generating the metabolite is reduced. The syndrome was initially described as an infectious mononucleosis-like illness in patients being treated for lepromatous leprosy.^{54,55} Patients present with fever, malaise, a generalized cutaneous eruption, lymphadenopathy, and hepatitis. The skin eruption can range from maculopapular to toxic epidermal necrolysis and the hepatitis shows a mixed hepatocellular and cholestatic pattern.^{52,55,56} Patients often have leukocytosis, peripheral eosinophilia, and atypical lymphocytosis. Although most patients recover with discontinuation of the drug, fatalities have been reported. Systemic corticosteroids have been used in this syndrome; however, the benefit of this treatment is unclear. Some patients have been reported to develop hypothyroidism several months after a hypersensitivity reaction.⁵⁷

Cutaneous hypersensitivity eruptions Dapsone has been associated with a wide variety of skin eruptions, ranging from the typical maculopapular drug eruption to erythema multiforme and toxic epidermal necrolysis.⁵⁴ Photosensitivity has been reported in some patients taking dapsone, often in the context of the dapsone hypersensitivity syndrome.⁵⁸

Carcinogenesis Dapsone has been suggested to be a weak carcinogen.⁵⁹

Pregnancy and lactation Although dapsone has not been proven safe in pregnancy, recent series of patients with linear IgA dermatosis and patients with leprosy suggest

that dapsone can be safely used in pregnancy.^{8,60,61} However, dapsone is secreted in breast milk and can rarely cause hemolytic anemia in breast-feeding infants of mothers on dapsone.⁷

Drug interactions

Probenecid can reduce the renal excretion of dapsone. Rifampicin can also decrease the functional half-life of dapsone secondary to induction of metabolizing liver enzymes.⁹ Similarly, increased oxidative stress to the erythrocyte due to concomitant use of other oxidative drugs e.g. other sulfonamides and antimalarials may worsen the hemolysis that is normally seen with dapsone.⁶²

Pretreatment considerations

The most important step in minimizing the toxicity associated with dapsone therapy is to evaluate the patient before initiating the drug and providing close follow-up. Patients candidate for therapy with dapsone should be screened for significant preexisting cardiopulmonary disease that would increase their risk if significant hemolysis or methemoglobinemia were to develop. Lower initial doses are recommended in these patients. Preexisting anemia, liver, or kidney disease offers a more narrow therapeutic window and requires closer laboratory monitoring. A CBC with differential, liver, and renal function testing should be performed prior to initiating therapy.

A G6PD level should be determined. A screening test for G6PD deficiency may be falsely normal if the patient has an elevated reticulocyte count, is heterozygous for the enzyme deficiency, or has a variant of the

enzyme that is less capable of handling oxidative stresses in red cells. Particular attention should be paid to the patient's baseline hemoglobin level. Patients that have a preexisting mild iron, folate, or vitamin B12 deficiency will not be able to mount an adequate reticulocyte response to the initial dapsone-induced hemolysis, leading to a more significant hemolytic anemia.⁶³

Therapeutic guidelines

Most patients require 100-200 mg/day for adequate control of their skin disease. Patients can be started on lower doses; however, it will take longer to determine if dapsone is effective for their skin disease. Dapsone doses can be adjusted at 2-week intervals until complete control of the skin disease is obtained, while monitoring for dose dependent adverse events. In patients under good control, it is recommended that the dapsone dose be gradually decreased to the lowest effective dose to minimize adverse effects.

Conclusion

Dapsone has proved to be the mainstay of therapy for the management of DH, LABD, and the bullous eruption of SLE. In addition, it has proven useful in a wide variety of other immunobullous diseases. Adverse events can be minimized by a complete understanding of the pharmacology of the drug and of which diseases are most likely to respond to treatment with dapsone.

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