Review Article

Dapsone in dermatology: a comprehensive review

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Introduction

Not many drugs have withstood the test of time. Some were found to be less efficacious, whereas others have fizzled out due to intolerable or serious side effects. However, certain drugs are still being used since discovery. A few examples are metformin, and relevant to dermatology, methotrixate and dapsone. The main groups of systemic drugs used in dermatology include antibacterials and a variety of anti-inflammatory agents and an impressive group of immunosuppressives. Since dapsone exhibits all of the above properties, it is still being used widely in dermatology worldwide.

Though dapsone was first synthesised in 1908, researchers only became interested in the drug after the discovery of the sulphonamide, prontosil, the first sulphonamide antibiotic to be discovered. The award of the Nobel Prize for Medicine for this discovery resulted in widespread interest in other related compounds. 4-diaminodiphenylsulfone is the chemical name of dapsone. To date, it remains the prototypic drug of sulfones.

Though structurally related, the two groups are metabolized differently by the human body, hence their side effects differ. Other sulphur-containing compounds are sulphonylureas and thiazide diuretics. Dapsone was first used to treat streptococcal infections using a very high dose (1-2 g daily). The discovery of its antimycobacterial property in animals led to its widespread use in treating leprosy, a disease with a worldwide prevalence. In fact, dapsone was used for decades as monotherapy for leprosy. Though bacteriostatic, dapsone remains a principal drug in multi-drug regimens for leprosy to date. Since then, it has also been used as an antiparasitic agent (pneumocystic jeroveci and malaria as well).

Sulphapyridine, a sulphonamide, was successfully used in 1947 to treat dermatitis herpeteformis (DH). Subsequently, dapsone became the drug of choice for the treatment of DH.

Since dapsone is widely used by dermatologists in Sri Lanka, a better understanding of its pharmacology, mechanism of action and mechanisms by which it causes damage to human tissue should result in its proper use and will allow us to maximize the therapeutic benefits. It will also prevent/minimize the significant adverse effects and relieve the phobia some have about this valuable drug.

Pharmacology

Dapsone is highly lipophilic and is therefore readily absorbed from the intestines and easily penetrates into human tissues. It penetrates well into all the cells of the human body. Peak concentration is reached within 2-8 hours. The elimination half-life is fairly long (1-1.5 days). This allows daily dosing. The metabolites of the drug remain in circulation as long as 30 days after the last dose. The latter is important in managing dapsone hypersensitivity syndrome.

Dapsone's incomparable effectiveness compared to other members of the sulfones and sulphonamides is due to its superior absorption and easy penetration into most cells, including activated neutrophils and mononuclear cells. Hence its indisputable efficacy in many granulomatous infectious disorders like leprosy. Dapsone is excreted in breast milk and crosses the blood-brain barrier. However, its widespread use in leprosy in developing countries has proven its safety in pregnancy and lactation.

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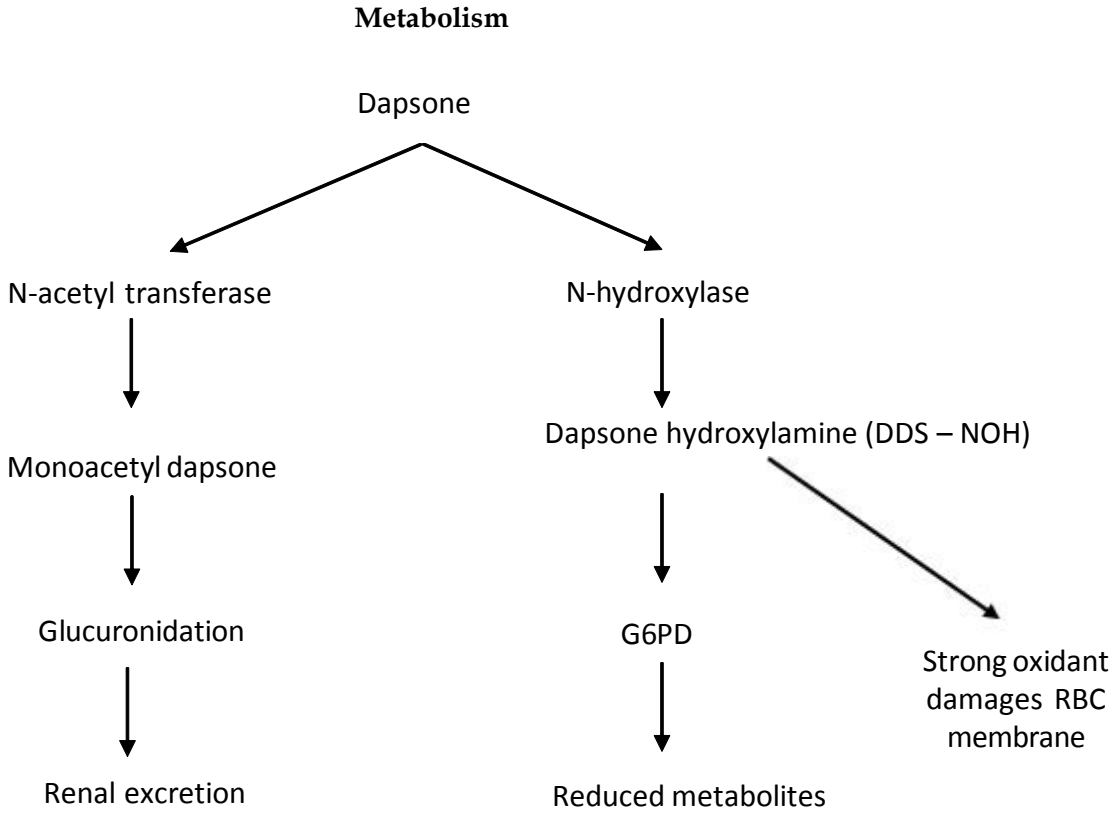


Metabolism

In order to excrete a lipophilic drug like dapsone, it needs to be converted to a hydrophilic compound. This process (biotransformation) also results in generation of reactive intermediate metabolites (bio-activation).

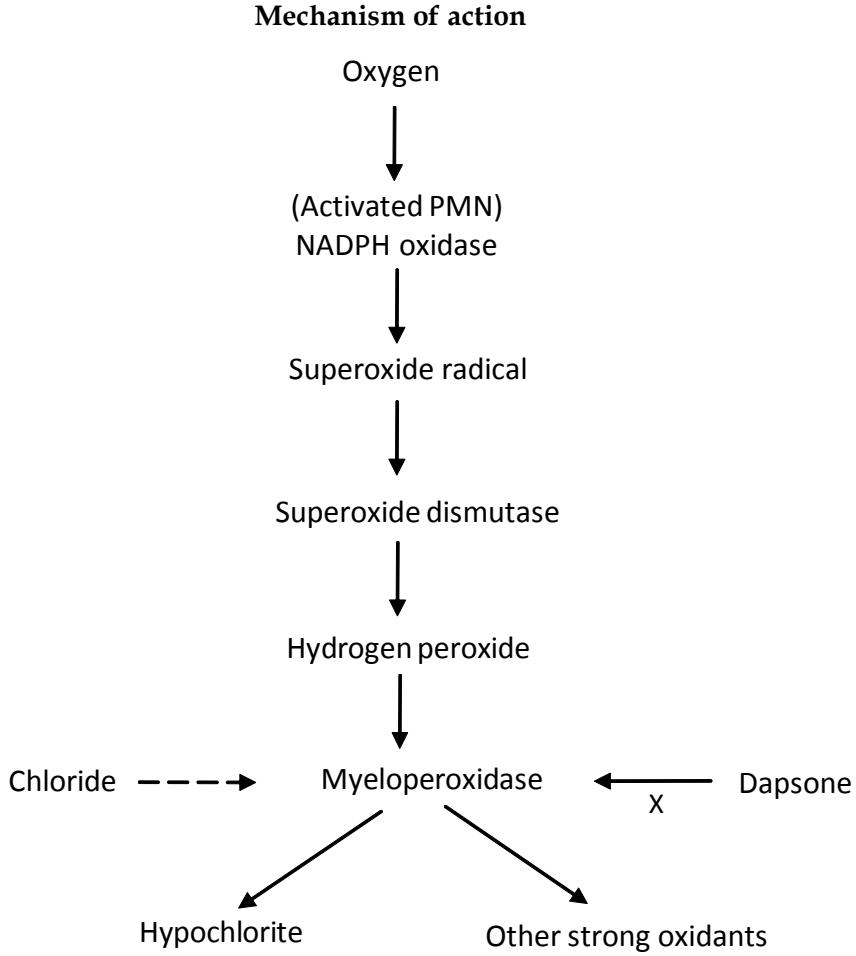
As shown above, dapsone is reversibly acetylated in the liver by N-acetyl-transferase to N-acetyl-dapsone (MADDS) and deacytelated back to diaminodiphenylsulfone (DDS). As a result, a state of equilibrium develops between these two compounds.

The second metabolic pathway of dapsone is hydroxylation. This is a phase I drug metabolic pathway mediated by cytochrome P-450 enzymes (CYP-450). This process of hydroxylation generates dapsone hydroxylamine (DDS-NOH). Unlike acetylation, hydroxylation also takes place, a part from the liver, in keratinocytes and also by polymorphonuclear leukocytes and mononuclear cells. DDS-NOH is the most effective metabolite of dapsone therapeutically it is a potent anti-inflammatory and antibacterial compound. Unfortunately, the same compound is responsible for dapsone's adverse effects.

Dapsone undergoes significant enterohepatic circulation. Dapsone can be safely used in both liver and renal failure with minor dose adjustments. Dapsone is well-absorbed in dermatitis herpetifomis (DH) despite the presence of gluten-sensitive enteropathy.

Excretion

Dapsone and its metabolites are conjugated in the liver and rapidly excreted as dapsone glucuronide by the kidneys.



Mechanism of action

Dapsone has both antimicrobial and inflammatory properties, the latter by several mechanisms.

As can be seen, myeloperoxidase plays an important role in quenching the harmful effects of O_2-free radicals generated by neutrophils, eosinophils and monocytes. The latter cells play a key role in granulomatous dermatitis.

The main antibacterial effect of dapsone is by inhibition of dihydropteroate synthetase, a key initial enzyme in folic acid utilization.

Since dapsone, therapeutic benefit is well-established in neutrophilic dermatoses. It is reasonable to argue it affects a number of key inflammatory pathways of neutrophils. These include:

1. Myeloperoxidase – halide mediated cytotoxicity (part of neutrophil respiratory burst). As a major scavenger of reactive O_2 species, dapsone reduces both H_2O_2 and free hydroxyl radicals. It is well-known that neutrophil-mediated skin damage occurs in linear IgA disease, bullous SLE, DH and Sweet's syndrome. Dapsone's therapeutic benefit in these conditions has been proven beyond a doubt worldwide. Similarly, corticosteroids too may have anti-neutrophilic effects and can be used to contribute for a better therapeutic effect. Both can be used concomittantly for an additive effect.
2. Neutrophil chemotaxis
Dapsone binds to intergrins on the neutrophils and inhibits adherence to endothelial cells, thereby preventing chemotaxis. It is also believed to inhibit LT4-mediated neutrophil chemotaxis.
3. Neuroprotection
Recent research indicates that dapsone can influence functions of the central nervous system. Its neuroprotective function is well-seen in stroke patients, and is believed to be mediated by its antioxidative and anti-convulsive properties. Of special interest is its benefit in neuro-Sweet's syndrome. Additionally, it is also known to inhibit the growth of glioblastomas.

Over the years, dapsone has been established as a very useful drug for dermatologists of the entire world. Currently, no other drug used in dermatology exhibits such a wide array of benefits. Among these are:

1. A combination of anti-inflammatory, anti-microbial and anti-protozoal effects.
2. Its proven safety in children, adults, the elderly and in pregnancy.
3. Safety of long-term treatment (once used as life-long monotherapy of leprosy patients).
4. Unique, powerful disease-specific effects on dermatitis herpeteformis.
5. Fast relief of loxoscelism associated with brown recluse spider bites.
6. Its safety in combination with other drugs, e.g. multi-drug therapy for leprosy, steroids.
7. Its free availability and very low cost.

Clinical uses of dapsone

Indications

Dapsone is currently used worldwide in the treatment of neutrophilic/eusinophilic/monocytic (granulomatous) mediated skin diseases and in the treatment of leprosy, the latter as the World Health Organization's multi-drug therapy regimens (MDT). It can be used as monotherapy or as part of combination therapy. Its main indications are:

1. As monotherapy, benefits proven beyond doubt
   - A) Dermatitis herpetiformis
   - B) Linear IgA disease
   - C) Infantile acropustulosis
   - D) Erythema elevatum diutinum
   - E) IgA pemphegus
   - F) Subcorneal pustular dermatosis
2.
   - A) As combination therapy, along with other immunosuppressives, especially oral steroids
     1. Sweet's syndrome
     2. Bullous pemphigoid
     3. Bullous SLE
     4. Eosinophilic folliculitis
     5. Leucocytoklastic vasculitis
     6. Pyoderma gangrinosum
     7. Pemphegous vulgaris
     8. Relapsing polychondritis
   - B) In combination with other antimicrobial/ antiprotozoal agents
     1. Leprosy
     2. Pneumocystis jeroveci infection in AIDS
     3. Malaria

Dosage of dapsone in dermatology

Fixed dose regimens of WHO blister packs makes its use easier in leprosy. The newer uniform multi-drug therapy further simplifies its use. However, in other inflammatory skin diseases, its dosage should be one of a minimum required to control the disease activity. Initial dosage in adults ranges from 50 to 100 mg daily. A higher dose upto 300 mg per day can be tried after 4 to 6 weeks of low dosage therapy. However, this will depend on the tolerability and monitoring laboratory results. Once control of the disease is achieved, the dose can be reduced to one of maintenance.

For children, tablets can be crushed and dissolved in a sweet syrup. The general recommended dose is 2 mg/kg/day, doubled if necessary after four weeks.

Adverse effects

Adverse effects to dapsone are of two types – pharmacological and idiosyncratic. The first is dose-dependent, and the latter dose-independent, therefore the latter cannot be predicted.

Pharmacological adverse effects

The two most commonly encountered types are haemolysis and methaemoglobinaemia. As said earlier, these are often encountered side effects and can be severe at a higher dosage exceeding 100 mg daily. Dapsone per se is not harmful to red blood cells. However, its red cell toxicity comes from its N-hydroxy metabolites (N-hydroxy-dapsone-hydroxylamine and N-hydroxy-monoacetyl-dapsone-hydroxylamine). These are potent oxidants, produced in the liver by the cytochrome P-450 (CYP) system. As red blood cells have lost their nuclei, they do not synthesise new molecules. Their survival depends on cell membrane integrity carried out by the anti-oxidant system glutathione, the hexose monophosphate pathway and glycolysis providing energy to glutathione in a reduced state.

Haemolysis

For the aforementioned reasons, older red blood cells are especially vulnerable to oxidative stress and undergo destruction. This is seen in all patients

receiving dapsone within the first few days. The resultant drop in haemoglobin stimulates the bone marrow to release young red blood cells (reticulocytes) into circulation. This may lead to a falsely low HbA1C in poorly-controlled diabetic patients. As N-hydroxy-metabolites are potent oxidants, they pose a persistent oxidative on the RBCs. The resulting depletion of reduced glutathione leads to the formation of glutathione disulphides, altering the red cell membrane pliability, Heinz body formation and subsequent splenic destruction.

Lipid peroxidation is another mechanism of RBC membrane alteration leading to early destruction. The above mechanisms significantly differ in individual patients. This is specifically dependent on the amount of glucose 6-phosphate dehydrogenase enzyme levels. A significant variability of G6PD levels is found in all races. People who are severely lacking the above enzyme will develop acute severe intravascular haemolysis. Cimetidine in high dosage is known to reduce the risk of this side effect.

Methaemoglobinimia

The second major haematological side effect is methaemoglobinimia. This too is caused by the N-hydroxy-metabolites. This too is dose-dependent. In patients taking small doses of dapsone, the amount of methaemoglobin produced is insignificant. Methaemoglobin reductase in RBCs reconverts methaemoglobin to haemoglobin. Patients taking higher doses of dapsone produce significant amounts of methaemoglobin. As methaemoglobin has less capacity to carry oxygen, higher levels of methaemoglobin can result in a state of hypoxia. This is especially severe in patients who are anaemic or have compromised cardiopulmonary functions.

Idiosyncratic adverse effects

Agranulocytosis is the most lethal idiosyncratic adverse effect of dapsone. Though the exact mechanism is unclear, it is believed to be caused by N-hydroxylamine metabolites destroying the neutrophil precursors in the bone marrow. Fortunately, this is rare, with an incidence of 65 cases per 10^6 patient years. It is commonly encountered in patients treated with dermatitis herpeteformis and very rarely encountered in leprosy patients. There is no clear explanation for this difference. Agranulocytosis is encountered between the third and twelfth weeks of treatment. Early leukopenia, if seen, necessitates early stoppage of treatment.

Peripheral neuropathy

Rarely, prolonged treatment with dapsone is associated with a distant motor neuropathy. Rarely, they may also have sensory symptoms. Clinically, both short exposure of high dosage (1.2 g for 7 days) or low-dose prolonged exposure (150 mg for 5 years) are known to cause this. Fortunately, most patients recover on withdrawal of the drug, but symptoms may last upto two years. Though the exact mechanism is unknown, it is believed to be caused by axonal degeneration. Other neurological manifestations include optic atrophy (overdosage) and acute psychosis.

Gastrointestinal adverse effects

These are often mild and well-tolerated, allowing continuation of treatment. They are often encountered in the early phases of treatment. These adverse effects include nausea, anorexia and vomiting. Rarely, dapsone is known to cause pancreatitis and gall bladder perforation.

Dapsone hypersensitivity syndrome (sulfone/ dapsone syndrome)

Typically, patients present with fever, a generalized erythematous maculopapular rash and jaundice seen between the third and twelfth weeks of treatment. The jaundice is mainly due to the liver damage and partly due to haemolysis. Rarely, more severe cutaneous reactions are seen, including Stevens-Johnson syndrome or toxic epidermal necrolysis. The liver injury is a variable mixture of hepatocyte damage and cholestasis. A peripheral blood eosinophilia is often seen. Rarely, auto-antibodies (ANA) may become positive. All patients suffering from this syndrome require immediate withdrawal of all drugs, hospital admission, exclusion of other forms of liver disease and a prolonged course of oral steroids to cover the effects of dapsone metabolites in circulation, which may last upto 6 weeks from the last dose. Patients may also require supportive therapy in the event hepatic synthetic functions are compromised. Examples include albumin transfusions and administration of vitamin K. As these patients often have severe vomiting, they may require intravenous fluids as well as intravenous steroids, especially during the first week of treatment. In paucibacillary leprosy, they may not require further treatment with anti-leprosy drugs. This is because the N-hydroxy-metabolites of dapsone, the cause of hypersensitivity, are also lethal to the few organisms in paucibacillary leprosy. Many a dermatologist has observed the disappearance of skin lesions of paucibacillary leprosy patients once they recover from dapsone hypersensitivity syndrome.

Photosensitivity

Some patients on long-standing dapsone therapy may develop mild photosensitivity. However, this usually settles with photoprotection and the use of a mild topical steroid.

Drug interactions

Drug interactions are relatively uncommon. The most important ones are outlined below.

Dapsone monitoring guidelines

Baseline
History and examination Complete history and physical with emphasis on cardiopulmonary, gastrointestinal, neurological, hepatic and renal systems ***Laboratory*** Full blood count with differential WBC count Liver function tests (particularly AST/ALT) Renal function tests Urine full report (UFR) Glucose-6-phosphate dehydrogenase level (G6PD)
Follow-up
History and examination Each visit reassess peripheral motor neurologic examination Each visit assess for signs and symptoms of methemoglobinemia Question for any other significant adverse effects ***Laboratory*** FBC with differential WBC count every week for 4 weeks, then every 2 weeks until week 12, then every 3-4 months Reticulocyte count as needed to assess degree of response to dapsone hemolysis Liver function tests every 3-4 months (particularly AST/ALT) Renal function tests and urinalysis every 3-4 months Methemoglobin levels as clinically indicated

By proper pre-treatment evaluation and subsequent careful and proper follow-up, toxicity can be minimized and treatment outcomes can be optimized. As suggested, G6PD levels should be obtained whenever possible in all patients. It is important to realize that G6PD levels may be falsely normal in patients who have an elevated reticulocyte count or have a genetic variant that is less capable of handling oxidative stresses on the RBC. The genetic heterogeniety of G6PD deficiency means that patients of different G6PD levels may respond differently to the same dose of dapsone. However, in remote areas, dapsone can be given in the absence of G6PD screening.

Measurement of haemoglobin is of critical importance in all patients receiving dapsone during early periods of treatment. As leprosy is prevalent among poorer communities, who also suffer from mixed-deficieny anaemia, it is important to correct the deficiency before commencing dapsone, otherwise the compensatory bone marrow response to dapsone-induced haemolysis will be significantly reduced, resulting in severe anaemia. Similarly, a poor reticulocytic response may indicate an underlying deficiency state rather than poor compliance.

Summary

Dapsone is an important drug for dermatologists worldwide. One should be fully conversant with its clinical uses. It should not be avoided out of fear of its side effects. Instead, one should use it carefully. Since both pre-treatment evaluation and subsequent follow-up require simple clinical skills and simple haematological testing, the drug can be used even in remote areas. To facilitate this, a dapsone card can be issued to each and every patient receiving dapsone. The one that is used in Lady Ridgeway Hospital is shown in the diagram. This summarizes all aspects relevant to its use and outlines urgent measures that have to be taken in the event of an adverse effect.

Dapsone Card

Name:

Address:

Age:

DR's contact cell phone no's

Indication for therapy:

Combined therapy

Monotherapy:

Specify

Date of commencement of treatment:

Fixed ☐

Non Fixed ☐

Dosage:

Pre treatment assessment

Cardio pulmonary status:

Consanguinity:

Past history of allergies:

Drug induced haemolysis:

Base line parameters:

- G6PD level (Screening / quantitative):
- Haemoglobin / Retic count:
- WBC/DC:
- Platelets:
- Methaemoglobin reductase levels:
- AST:
- ALT:
- Serum albumin

Follow up assessment

	Hb/Retic Count	WBC	PLT	AST	ALT	Meth Hb levels
1st Week						
1st Month						

Use with caution the following drugs:

Atropine, Bupivocaine, Lidocaine, Mepivacaine, Prilocaine, Xylocaine, Ciprofloxacin, Pyrimathamine, Sulfadoxine, Trimethoprim, SMX-TMP, Sulfonamide

Advice

- Treatment should be stopped immediately if patient develops fever, rash, yellow eyes (dapsone hypersensitivity syndrome) or patient becomes acutely breathless (Methaemoglobinemia) Refer guideline
- Drugs to be avoided
  Methotrexate
  Co trimoxazole
  Hydroxychloroquine
  (Worsens the hematological side effects)
- The drug to be taken after dinner
- Pregnancy, lactation, immunization not contraindicated