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Dapsone in Dermatology

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ABSTRACT

Dapsone is a systemic drug that is used for its anti-inflammatory properties in dermatology. The diseases in the therapeutic spectrum of Dapsone are neutrophilic dermatoses (Sweet Syndrome, Pyoderma Gangrenosum, Erythema Elevatum Diutinum, Subcorneal Pustuler Dermatosis and Behçet's Disease), immunobullous diseases (bullous pemphigoid, dermatitis herpetiformis, bullous SLE, linear IgA dermatosis and pemphigus vulgaris), chronic urticaria, acne vulgaris and eosinophilic folliculitis. It has possible hematologic, neurologic and psychiatric, gastrointestinal and renal side effects.

INTRODUCTION

Dapsone belongs to the sulphones group and is a synthetic derivate of anyline [1]. Another nomenclature of dapsone is 4,4'-diaminodiphenylsulfone. It has been discovered in 1937 for its antibacterial properties; however soon after it was started to be used for its anti-inflammatory properties as well. Not only dapsone has anti-inflammatory properties; but also, its metabolites exert anti-inflammatory properties [2]. Dapsone inhibits the migration of neutrophils to the inflammatory lesions, along with inhibiting the movement of neutrophils out of the circulatory system. Furthermore, it prevents the respiratory burst of neutrophils, leading to decreased tissue destruction [3]. Dapsone is mainly used in neutrophilic and eosinophilic dermatoses; it is also used in a variety of inflammatory non-dermatologic disorders. It is a popular drug for its steroid sparing effects in inflammatory diseases [2].

The dermatological uses of dapsone can be summarized as follows; neutrophilic dermatoses (Sweet Syndrome, Pyoderma Gangrenosum, Erythema Elevatum Diutinum, Subcorneal Pustuler Dermatosis and Behçet's Disease), immunobullous diseases (bullous pemphigoid, dermatitis herpetiformis, bullous SLE, linear IgA dermatosis and pemphigus vulgaris), chronic urticaria, acne vulgaris, eosinophilic folliculitis and the historical use in leprae.

ADVERSE EFFECTS

Dapsone may lead to both local and systemic side effects. Most commonly involved systems are the hematopoietic system, the skin and the gastrointestinal system [4]. The side effects are divided into dose dependent and dose independent subgroups. Hematologic, neurologic and psychiatric, gastrointestinal, renal side effects are also reported. No studies showed a relationship between dapsone and increased risk of malignancies, unlike the other immunosuppressive drugs [1].

Methemoglobinemia

Methemoglobinemia is the most common adverse effect of the drug. The condition is not usually seen in low and moderate doses but may appear in high doses (>200 mg/day) [5]. The clinical signs and symptoms vary according to methemoglobin concentration. In low concentrations patient may complain of fatigue, dizziness, headache, tachycardia, and weakness. The presentation may be more intense in high levels of methemoglobin such as acidosis, cardiac dysrhythmias or hypotension, coma, dyspnea and convulsions.

Cyanosis may be evident when the methemoglobin concentration is 15% or more in blood. The cyanosis related to methemoglobinemia differs from the other causes of cyanosis by its color. The mucous membranes become brownish rather than blue. This definitive brown color is known as 'chocolate cyanosis' [6].

Hemolysis

Hemolysis is also a common side effect of Dapsone.

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Advanced age and increased daily consumption dose are associated with the severity of hemolysis. It is advised to stay in safe dose range which is 1.5 mg/kg per day [7].

Dapsone Hypersensitivity Syndrome (DHS)

DHS is a rare potentially life-threatening idiosyncratic systemic condition. DHS symptoms usually initiate within 2-6 weeks after the administration of dapsone. However, the symptoms may appear within 6 h in the previously sensitized patients and may be seen as late as 6 months after dapsone treatment [8]. Clinical manifestations are high fever, skin rashes, lymphadenopathy, eosinophilia and exfoliative dermatitis. Anemia, pulmonary, renal and hepatic involvements are also probable [9]. A review by Lorenz revealed that the frequency of DHS was 1.4% and fatality rate was 9.9% [10].

Miscellaneous

Adverse Gastrointestinal (GI) side effects are nausea and vomiting, weight loss and abdominal discomfort. Abnormal liver fuctions or biluribin tests, toxic or cholestatic hepatitis may also be observed. These findings may be related to DHS or may be isolated. Other rare adverse side effects include albuminuria, sleep deprivation, psychosis, electrolyte imbalances, atrioventricular block with unkown mechanisms [2].

DAPSONE IN PREGNANCY

Dapsone is category C in pregnancy [2].

1. Neutrophilic dermatoses

1) **Sweet Syndrome:** Sweet syndrome is the most commonly observed subtype of febrile neutrophilic dermatoses. The typical presentation is erythematous and painful papules, plaques or nodules and increased number of neutrophils in the peripheral blood smear. Most commonly involved sites are the face, neck and upper extremities. The exact etiology of classical sweet syndrome is unknown but it may be associated with infections, drug use, pregnancy or inflammatory bowel disease. In addition, the disease may occur due to malignancy as well; most commonly hematologic malignancies [11]. The lesions of sweet syndrome may persist weeks to months if untreated. The first line treatment modalities for the disease are systemic and intralesional steroids, potassium iodide and colchine. The second line treatment modalities include indomethacin, clofazimine, cyclosporine and dapsone. Antibacterial, cytotoxic agents and tumor necrosis factor-alpha blockers can also be used in refractory cases [12].

   Neutrophilic dermatosis of the dorsal hands is very similar to sweet syndrome morphologically and histopathologically; and in fact, it is considered as a localized and rare subtype of this entity [13-15]. A case report by Ramos [16] demonstrated that 100 mg/day dapsone use is effective in the treatment of neutrophilic dermatosis of the dorsal hands.

2) **Pyoderma Gangrenosum:** Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis and the etiology is not fully understood to date. The clinical presentation is recurrent painful cutaneous ulcers without definite borders and a circumferential erythema. However, it should be remembered that the diagnosis is made by exclusion. Ulcerative, pustular, bullous and vegetative forms are the most common subtypes [17] Local and systemic steroids, cyclosporine, tacrolimus, infliximab, dapsone, and sulfasalazine may be used in medical treatment of PG [18]. Din [19] reported a retrospective review concerning the use of dapsone in pyoderma gangrenosum patients. Among the 27 patients who were treated with systemic dapsone for a minimum of four weeks interval, 15.6% showed complete clearance of the lesions whereas 81.3% showed partial improvement, and 1 patient did not benefit from dapsone therapy at all. A study conducted by Li [20] revealed that the topical use of dapsone is effective in the treatment of pyoderma gangrenosum. Twenty-one patients were included to the study and 85.7 percent of the patients responded partially to 5% dapsone cream and 9.5 percent of the patients responded completely. Treatment response required a minimum of 4.3 weeks and the average of treatment duration was 14.6 months. None of the patients reported side effects.

3) **Erythema Elevatum Diutinum:** Erythema elevatum diutinum is a cutaneous vasculitis of unknown etiology with sterile neutrophilic infiltrate in the histopathology. The disease presents with erythematous violaceous papules and nodules that are symmetrically distributed on the dorsum of the elbows, knees, ankles and hands; surface hyperkeratosis is a clue in the diagnosis [21]. In addition, this entity may occur in the course of HIV infections [22]. Dapsone is the first-choice treatment in erythema elevatum diutinum. The chemical can be used both topically and systemically. A review by Momen [23] showed that dapsone was effective as a single agent in 80 percent of the cases. Local use of dapsone was also efficient in achieving clearance of the lesions, with a preferable side effect profile. A case report by Cardis [22] demonstrated that dapsone may lead to severe headaches which may be a reason for drug discontinuation.

4) **Subcorneal Pustuler Dermatosis (Sneddon Wilkinson disease):** Subcorneal pustuler dermatosis is an uncommon benign disease with an unclear exact etiology. The disease commonly occurs in trunk and intertriginous regions. The clinical presentation is flask sterile pustules emerging into annular plaques [24].

Dapsone is a first line treatment in subcorneal pustuler dermatosis. The other choices are sulphapyridine, colchicine, minocycline, cyclosporine and phototherapy. In addition, topical or systemic steroids may be administered [25]. The daily oral dapsone dose is 50-200 mg [26]. Topical dapsone therapy is a new approach in the treatment of subcorneal pustuler dermatosis, with a milder side effect profile which makes it useful in the elderly population. Doolan [27] reported a case of 82 years old subcorneal pustuler dermatosis patient who was unable to receive oral dapsone treatment due to decreasing hemoglobulin in the follow up visits. This patient was treated with topical dapsone 7.5% gel once daily. The lesions ceased completely after three weeks of therapy.

5) **Behçet's Disease:** Behçet's Disease is an acute but recurrent inflammatory disorder with multisystem manifestations. The major symptoms of Behçet's Disease are oral and genital ulcers, uveitis and other skin manifestations such as erythema nodosum and ostiofolluculitis [28]. Dapsone is effective as an oral agent at 100 mg/day dosage in the treatment of persistent aphthae and mild to moderate skin manifestations of Behçet's disease. However, it is non-effective if the mucocutaneous manifestations are severe [29]. In a study by Sharquie [30] urogenital ulcers, erythema nodosum and furuncles subsided in a few weeks under 100 mg/day oral dapsone therapy. However, two patients suffered of flares upon drug cessation. Thus, Dapsone is a treatment alternative for the mucocutaneous manifestations of Behçet's Disease at 100 mg/day oral dosage in mild to moderate cases.

2. Bullous Diseases

1) **Bullous Pemphigoid:** Bullous Pemphigoid (BP) is the most common type among blistering diseases which usually seen in elderly ages. Intake of drugs such as antidiuretics and antiepileptics, advanced age and neurological diseases are some of the risk factors. The clinical manifestations vary significantly but generally intensely pruritic erythematous eruption with widespread subepidermal blister formation is present [31]. According to the European Academy of Dermatology and Venerology guidelines about the treatment of bullous pemphigoid which was published in 2015, the treatment modalities are divided into two groups: widespread and local disease. In local disease, topical suprapotent corticosteroids are the first line treatment choice, whereas systemic corticosteroids, tetracyclines combined with nicotinamides, dapsone, sulphanamides and topical immunomodulators are the second-choice treatment options. In widespread disease, topical and systemic glucocorticoids are the treatment of choice. Azathioprine, mycophenolate, tetracycline+nicotinamide, methotrexate and chlorambucil are the second line therapeutic options. The dosing regimen of dapsone for bullous pemphigoid is 1 to 5 mg/kg/day administered orally [32]. According to Zychowska, dapsone is an effective steroid sparing agent in the treatment of bulluos pemphigoid [33] Previous studies focusing on the efficacy of dapsone revealed that dapsone monotherapy is efficacious in 20-45.5 % of the patients, 76% of the patients when combined with topical suprapotent corticosteroids and in 92-100% of the patients when combined with systemic corticosteroids [33-38].

2) **Dermatitis Herpetiformis (Duhring's Disease):** Dermatitis herpetiformis (Duhring's Disease) is a subepidermal blistering disease that typically manifests with pruritic plaques that resemble herpes lesions which are usually located at the extensor surfaces of the extremities. The disease often co-occurs with Celiac Disease of the small bowel [39]. The major treatment includes a gluten-free diet. Besides, systemic dapsone is the first line treatment modality starting with a dose of 50 mg/day orally, which can be increased up to 200 mg/day. It may be used up to 6 to 24 months, until the gluten free diet is efficacious. Possible side effects should be monitorized. Sulfasalazine, sulfapyridine, and sulfamethoxypyridazine can be used as second line treatment modalities if the patient fails to respond to dapsone treatment [40]. A case report by Burbidge and Haber showed that topical 5% dapsone gel is also effective in the treatment of dermatitis herpetiformis with a very tolerable side effect profile such as burning, itching, kserosisis and rash [41].

3) **Bullous SLE:** Bullous systemic lupus eritematosus (SLE) is an uncommon blistering disease characterized by subepidermal neutrophilic blisters that occurs as a complication in the course of SLE. The vesicles or bullae are tense and clinically appear like pemphigoid eruption. The disorder may present at any portion of the body: mucous membranes and skin itself [42]. This cutaneous complication is usually seen in young colored women at ages of 20-40 years [43]. The treatment options of cutaneous SLE and its complications are systemic steroids, dapsone, cyclophosphamide, mycophenolate mofetil, azathioprine, metothrexate, hydroxychloroquine, rituximab, colchicine and intravenous immunoglobulin. Dapsone can be used as a monotherapy or in combination with other immunosuppressants. De Risi-Pubgliese [44] demonstrated that dapsone is efficient in the treatment of bullous SLE; in their study the efficacy of dapsone was 90% and 23% of the patients complained of side effects.

4) **Linear IgA Bullous Dermatosis:** Linear IgA bullous dermatosis is a rare autoimmune blistering disease which is characterized by subepidermal blisters. The

disease can be both seen in childhood and adulthood. The clinical manifestations vary: erythematous papules, vesiculobullous lesions or urticaria-like plaques may be seen. The disorder may represent at the flexor surfaces of the extremities and the trunk as well as the extensor surfaces [45]. Dapsone is the first line treatment choice, like in dermatitis herpetiformis [46].

5) **Pemphigus:** Pemphigus is a group of autoimmune immunoglobulin G mediated vesiculobullous disease that manifests in the mucosal and cutaneous surfaces. The major subtypes of pemphigus are: pemphigus vulgaris, pemphigus foliaceus and paraneoplastic pemphigus. Systemic steroids are the first choice in treatment; since they have serious short- and long-term side effects a steroid-sparing agent is necessary for adjuvant treatment [47]. Azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil and dapsone are the choices of adjuvant treatment [48]. Dapsone can be used as a monotherapy or as an adjuvant treatment option in pemphigus vulgaris. In the literature a total of 13 reports with 37 cases were reviewed by Gürcan [49]. In those cases, dapsone was used as a monotherapy in the 16% of the patients with a daily dosage of 100-200 mg/day and the disease was under control in all of the patients. Dapsone was added to systemic steroids, at a daily dosage of 50-200 mg/day in 43% of the patients and was added to systemic steroids and other immunosuppressants in 41% of the patients. Including all the treatment regimens, 86% of the patients were responsive to dapsone treatment, 14% did not respond at all; 24% of the patients reported side effects however the side effects were serious enough to discontinue the drug in only 11% of the patients [49].

3. Chronic Urticaria

Chronic urticaria is a frequent and heterogenous disease that may decrease the quality of life. Antihistaminic drugs and omalizumab are the leading drugs in treatment [50]. Cyclosporine is an alternative treatment for unresponsive patients. The approximate percentage of success with these three agents is 93. For the unresponsive patients, dapsone is also a choice [51]. A clinical trial by Liang [52] included 79 patients with chronic urticaria receveing dapsone treatment. Of these patients, 47% showed complete response to treatment and the time to achieve total clearance of symptoms was 5.2 months on average. After achieving complete response, dapsone dose was tapered on an average of 2.2 months in the 18 of the patients; only 8 of these patients re-applied with flares. Of all the 79 patients, only two reported serious adverse effects which were DRESS and methemoglobinemia [52].

4. Acne

Acne vulgaris is the eight most common disease world-wide, affecting the 9.4 percent of the general population. The most frequently affected age group is the adolescents. Male patients have a more serious course in particular [53]. The commonly used treatment modalities of acne vulgaris are topical retinoids and topical antibiotics, systemic antibiotics, hormonal therapies, systemic antibiotics and systemic retinoids- isotretinoin in particular [54]. Topical dapsone is a novel treatment alternative in acne vulgaris. There are two forms: 5% and 7.5% gel. A study conducted by Jawade [55] showed 31.54% treatment success with dapsone 5% gel in the 12th week of treatment. Inflammatory lesions resolved in 63.1% of the cases whereas non-inflammatory lesions showed 52.4% clearance. Dapsone gel was well tolerated and minimal side effects such as discomfort were observed. A placebo-controlled multi-centered randomized study held by Gold [56] demonstrated that among 1044 patients treated with 7.5% dapsone gel once daily, 55.5% of the inflammatory lesions cleared and 44.4% of the non-inflammatory lesions cleared. Overall, 48.7% of all lesions cleared at the 12th week of treatment. None of the patients reported any side effects [56]. A case report by Al-Kathiri [57] investigated the use of systemic dapsone in nodulocystic acne which is unresponsive to oral isotretinoin and steroids. Oral dapsone was administered at 100 mg/day along with topical benzoyl peroxide 2.5% for 4 months. 50 mg of dapsone was given for another two months. After a total of 6 months treatment, the resolution of nodulocystic acne lesions was observed and the first-year control visit, no recurrence was seen. No side effects were reported [57].

5. Eosinophilic Folliculitis

Eosinophilic folliculitis is an uncommon cyclical disease presenting with folliculocentric papules, pustules or plaques. The disease can be observed in the head, trunk and limbs. There are four subgroups of the disease: classical (Ofuji Disease), infantile, HIV related and associated with hematologic diseases. Treatment options are patient-tailored: indomethacin, topical corticosteroids, narrow band UVB, both local and systemic steroids, dapsone and oral tetracyclines are the choices. Furthermore, treatment of the underlying disease also contributes to clinical improvement [58]. Anjaneyan [59] reported a case with Ofuji disease who is allergic to nonsteroids and therefore could not be treated with indomethacin, receiving systemic dapsone 100mg/day for 2 weeks. Complete resolution of lesions was observed.

6. Leprosy (Historical)

Human leprosy (Hansen Disease) has been almost eradicated therefore has historical importance. The disease is mostly caused by mycobacterium leprae. The clinical manifestations vary with the patients' immune status. Without treatment, the disease can cause permanent damage in the skin, nerves and eyes [60]. Dapsone is one of the mainstay treatments in leprosy. The other choices are pyrazinamides, rifamycine,

levofloxacin, moxifloxacin, kanamycin, isoniazide, gatifloxacin, ethambutol, cycloserine, clofazamine, bedaquiline and capreomycine [61]. The standard daily dapsone dose is 100mg/day for adults whereas 50 mg/day for children. The treatment duration is 6 to 12 months. It's important to note that none of these drugs should be used as monotherapy [62].

CONCLUSION

Dapsone is an important anti-inflammatory drug that has many different uses in dermatology. Different posologies and durations are used for different diseases. Its side effects are seen mainly in the hematopoietic and gastrointestinal systems.

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