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Clofazimine Therapy In Dermatology: Review.

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ABSTRACT

Clofazimine is the riminophenazine strongly liphophilic dye, has been extensively used for the treatment of leprosy but little knowledge of its mechanism of action and may be multifactorial. Due to its anti-inflammatory and antimicrobial properties, the drug has a number of dermatological indications other than leprosy such as atypical mycobacterial infections, pyoderma gangrenosum, sweet syndrome, necrobiosis lipoidica, Melkersson–Rosenthal syndrome, severe acne, pustular psoriasis, discoid lupus erythematosus, Lupus miliaris dissiminata faciae, granuloma faciale, Erythema dyschromicum perstans, morbihan disease. Clofazimine also possess antifungal property (lobomycosis). This article reviews all postulated mechanism of action, clinical experience in several skin disesases, side effect profile are summarized.

Keywords: Clofazimine, Dermatology.

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INTRODUCTION

Clofazimine initially known as B663 was synthesized in 1954 by Vincent Barry and co-workers for the management of tuberculosis, however drug was proved to be ineffective. Y.T Chang and colleagues identified its effectiveness against *Mycobacterium leprae* which causes leprosy in 1955 at the National Institutes of Health (Bethesda, MD) [1]. In 1962, Browne and Hogerzeil et al first reported efficacy of clofazimine in leprosy patients in Nigeria [2]. In 1969 Novartis (Basel, Switzerland) launched it in leprosy treatment under the brand name of Lamprene. The US Food and Drug Administration approved clofazimine as an "orphan drug" in 1986 [3].

Structure

Clofazimine is a riminophenazine dye which has a phenazine nucleus with an alkylimino (R-imino) group at position 2 and phenyl substituents at positions 3 and 10. Antimicrobial activity due to alkylimino group with varying contributions according to the number and type of halogen atoms on the phenyl substituents. [4, 5].

Mechanism of action

Antimicrobial action

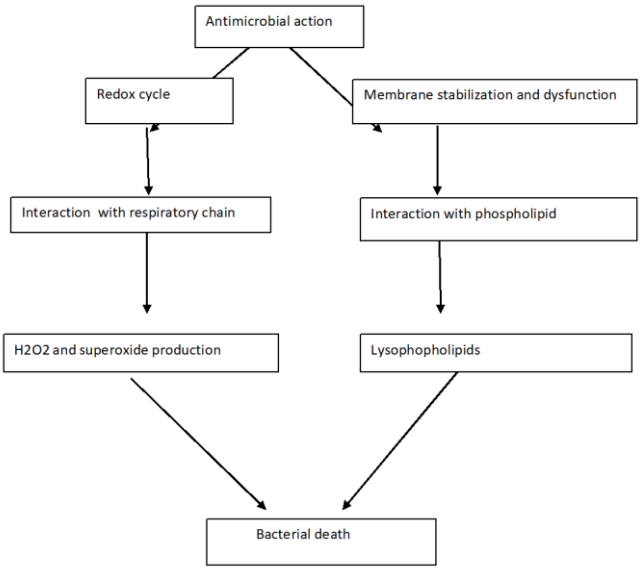
Redox cycling [6]

As clofazimine is highly lipophilic compound with redox potential it participates in intracellular oxidation of reduced clofazimine leading to generation of the antimicrobial reactive oxygen species (ROS) such as superoxide and H_2O_2

Membrane destabilization and dysfunction [7, 8]

Clofazimine interact with bacterial membrane phospholipid leading to generation of lysophospholipids, detergent-like agents with membrane-disruptive properties which are respomsible for bactericidal effects. Lysophospholipids interfere with potassium uptake and decrease in microbial ATP production.

Figure 1: Antimicrobial action of clofazimine

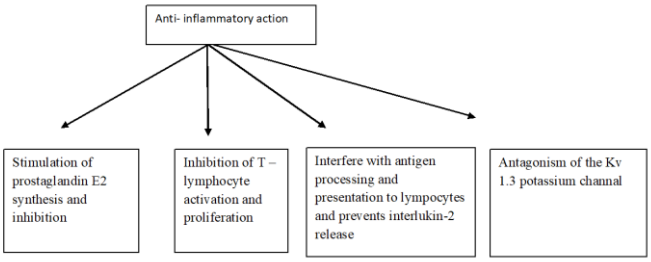


Anti-inflammatory action

- Stimulation of prostaglandin E2 synthesis and inhibition of neutrophil motility [8].

- Inhibition of T – lymphocyte activation and proliferation specifically Th 1 subtype of T-helper cells [8].
- Clofazimine accumulates in macrophage, interefere with antigen processing and presentation tolympocytes and prevents interlukin 2 release [8].
- Clofazimine interfered with Ca2+ signaling in T cells activated with the potent, non-physiological stimulus phorbol myristate acetate (PMA)/ionomycin, by antagonism of the Kv 1.3 potassium channel [8, 9].
- Bind to the guanine bases of bacterial DNA, therefore block the template function of the DNA and inhibit bacterial proliferation [10].

Figure 2: Anti-inflammatory action of clofazimine



Pharmacology and pharmacokinetics

Absorption

Absorption varies from 45% to 62 % following oral administration.[8]Clofazimine has low aqueous solubility, so orally administered in coarse crystalline form has very low bioavailability with inter individual variation in absorption kinetics. To enhance bioavailability administered as a microcrystalline suspension in an oil-wax base. Intake with fatty food improves absorption to 70% [11]. The product should be protected from humidity and heat. Its shelf-life is 5 years.

Distribution

After absorption into systemic circulation, rapid distribution occurs to peripheral compartments followed by re-equilibration into the central compartments leading to low steady state plateau after several months as a consequence of its extended half-life [12]. Clofazimine is a highly liphophilic compound tend to be deposited in the gastrointestinal tract, liver, bile, gall bladder, lungs, adrenals, kidneys, lymph nodes, muscle, bone, skin and subcutaneous fat, this results in a discoloration of the organs and skin [13].

In view of its very long half-life of almost 2 months and marked tissue storage, it retains its activity even when given on a daily or alternate basis. In fact, the basis of the monthly loading dose of clofazimine 300 mg given in adults along with the pulse dose of rifampicin in the World Health Organization (WHO) standard multidrug therapy in multibacillary leprosy is based on this principle [14].

Metabolism

Partially metabolism occur in the liver by cytochrome P450 isoenzyme CYP3A4/A5and CYP1A2 resulting in interaction with drug metabolized by CYP3A4 pathway [15].

Elimination

Excretion occurs in unchanged form in urine in negligible concentration (0.0 1-0.43%) while large proportion in faeces (35%) [16]. Three metabolites are identified in the urine. Hydrolytic dehalogenation of clofazimine forms metabolite I and metabolite II are formed by a hydrolytic deamination reaction followed by glucuronidation [17]. Small amount is also eliminated in the sputum, sebum and sweat [12].

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Uses (are listed in table 1)

Table 1: MB- MDT blister pack for 12 months (adult and children)

Drug name	Adult	Children 6-14 yrs	Children less than 6 yrs
• **Dapsone**	100 mg daily	50-100 mg daily	25 mg daily
• **rifamipicine**	600 once a month (supervised dose)	300-450 mg once a month (supervised dose)	150-300 once a month (supervised dose)
• **clofazimine**	300 mg once a month (supervised dose) and 50 mg daily	150 -200 mg once a month (supervised dose) and 50 mg alternative a day	100 mg once a month (supervised dose) and 50 mg twice a week

Table 2: Uses of clofazimine

Leprosy Type 1 reaction Type 2 lepra reaction (ENL) ENL not responding to steroid Severe ENL where use of corticosteroid is contraindicated Atypical microbial infection	Melkersson Rosenthal syndrome Granulomatous cheilitis Discoid lupus erythematous Necrobiosis lipodica Pyoderma gangrenosum Sweet syndrome Lupus miliria dissiminata faciae	Morbhian disease Erythema dyschromicus perstans Generalized pustular psoriasis Lobomycosis Babesiosis

Leprosy

Its accumulation within the macrophages inhibits multiplication of intracellular *M. leprae*. For the prevention of secondary dapsone resistance, clofazimine should be administered to lepromatous (LL) and borderline (BL, BB) leprosy patients in combination with dapsone and rifampicin. For the management of established dapsone resistance, clofazimine should be combined with rifampicin [12].

Recurrent type I reaction

Patients with recurrent type I reaction on face or those with persistent erythematous and edematous plaques or patches not responsive to steroids were treated with prednisolone and clofazimine who responded satisfactorily [18].

Erythema nodosum leprosum (ENL)

Anti-inflammatory properties of clofazimine in ENL patients was first observed by Browne in 1965 and this was subsequently confirmed experimentally by Vischer (19 69). Since then this additional effect of clofazimine in suppressing ENL has been confirmed by many workers, including Hastings and Trautman (1968), Imkamp (1968) and Warren (1968) [19-22].

Not responding to corticosteroids or where the risk of toxicity with corticosteroids is high [23]
Start clofazimine 100 mg three times a day for maximum of 12 weeks. Taper the dose of clofazimine to100 mg twice a day for 12 weeks and then 100 mg once a day for 12–24 weeks.

Severe ENL where use of corticosteroids is contraindicated [23]

Start clofazimine 100 mg three times a day for maximum of 12 weeks.
Taper the dose of clofazimine to 100 mg twice a day for 12 weeks.
100 mg once a day for 12–24 weeks.

Atypical mycobacterial infection

Clofazimine has high penetration in skin and soft tissue, so clofazimine-containing regimens plus amikacin, isepamicin, or bed aquiline are useful for management against NTM skin and soft tissue disease, like those caused by Rapidly growing mycobacteria (*M. abscessus* complex, *M. chelonae*, and *M.*

fortuitum)and slowly growing mycobacteria (*M. avium* complex, *M. kansasii* and *M. xenopi).* clofazimine has been used in the treatment of MDR and XDR TB as a category 5 agent [24].

Melkersson–Rosenthal syndrome

Clofazimine has been demonstrated to be effective for the management of Melkersson–Rosenthal syndrome. Sussman *et al*. reported complete remission in 5/10 patients and clinical improvement in 3/10 patients with MRS treated with clofazimine [25, 26].

Granulomatous cheilitis

Beneficial effect of Combination therapy with intralesional triamcinolone and clofazimine or dapsone seen in granulomatous cheilitis [27].

Discoid lupus erythematosus

Bezerra et al conducted a randomized clinical trial in which 17 patients with CLE (12 with DLE) were treated with chloroquine (250 mg daily) and 16 patients with CLE (14 with DLE) were treated with clofazimine (100 mg daily) added to sunscreen and oral prednisone. At 6 months, 82.4% of the patients in the clofazimine group experienced complete or almost complete resolution of the skin lesions, compared with 75% in the chloroquine group [28].

Necrobiosis lipodica

Benedix F et al reported a case report of ulcerated necrobiosis lipoidica that was resistant to various treatments, then managed with clofazimine, leading to complete remission within 5 months [29].

Pyoderma gangrenosum

Michaelsson *et al.* first time used clofazimine in 8 patient for pyoderma gangrenosum in 1976 at a dose of 300–400 mg/day with remarkable effect seen with rapid healing of lesion seen in 3 to 14 days [30]. Mensinget al reported good response at 200mg in 3 of 5 cases of PG [31]. Mohan et al report a case of Superficial Variant of Pyoderma Gangrenosum with uncontrolled diabetes mellitus showed clinical response to low-dose clofazimine [32].

Sweet syndrome

Von den Driesch et al in a study of 6 patients who had previously been unsuccessfully treated with methylprednisolone for chronic and relapsing sweet syndrome. They received an clofazimine 200 mg daily for 4 weeks and then 100 mg per day for 4 more weeks resulting in almost complete remission [33].

Granuloma faciale

Bajanca R et al published a 70 year-old woman of granuloma faciale from last seven years unresponsive to multiple medical and surgical treatments. Therapy with clofazimine with oral and intralesional corticosteroids led to the regression of the facial nodules [34]. Gomez-de la Fuente et al in a case report of granuloma faciale treated with clofazimine 300 mg daily for 5 months showed remarkable clinical response [35].

Lupus miliaris dissiminata faciae

Beneficial effect of clofazimine seen in lupus miliaris disseminatus faciei (LMDF) [36].

Erythema dyschromicum perstans

Piquero-Martin et al. 1989 conducted a clinical trial with clofazimine for management of erythema dyschromicum perstans, 7 of 8 patients treated with clofazimine obtained a good-to-excellent clinical response, but all of them showed side effects such as discoloration of the skin, xerosis ,

epigastralgia [37]. Later, another study conducted by Baranda et al in 1997 reported significant improvement in 4 out of 6 patients treated, where 2 patients dropped out of the study due to intolerable side effects [38].

Morbihan disease

Solid facial edema as complication of severe acne vulgaris treated with isotretinoin monotherapy and combination therapies of isotretinoin with either ketotifen or clofazimine all produced good results in morbihan disease [39].

Generalized pustular psoriasis (von Zumbusch)

Two cases of generalized pustular psoriasis successfully treated with clofazimine [40].

Other

Lobomycosis

Clofazimine acts as membrane pertubing agent in fungi, induces a cell membrane stress response and activates Pkc1 [41, 42].

Babesiosis

Clofazimine might also an alternative chemotherapeutic agent against human babesiosis caused by B.microti [42]

Table 3: Side effects of clofazimine

Skin-pigmentary changes – dark brown pigmenatation -Discolouration of sweat,hair,sputum,urine and feaces Gastrointestinal	nausea,vomiting ,abdominal pain -3 types of enteropathy: a.essinophilic/allergic pattern b.Crohn's disease like pattern with granulomas c.clofazimine-induced-crystal storing histiocytosis	Occular: -conjunctival deposition -crystal deposition in cornea -clofazimine crystals in tears

Adverse effect

Skin

Pigmentary changes -clofazimine induced pigmentation is reversible but takes months to years (1-2) to clear after completion of treatment. The initial reddish to reddish-blue color due to clofazimine which is a reddish -blue aniline dye deposit inside macrophage phagolysosome. The dark brown pigmentation develops later due to ceroid lipofuscinosis. On histopathological examination stains negative for melanin and iron. Clofazimine can produce a generalized pigmentation, which is more marked on sun-exposed areas [43].

Discoloration of sweat, hair, sputum, urine, and faeces may occur. General dryness of the skin, ichthyosis, pruritus, phototoxicity, acneiform eruptions, and non-specific skin rashes have also been observed.[12]

Gastrointestinal side effect

Most common GIT side effects are nausea, vomiting, abdominal pain usually epigastric, but occasionally described as " abdominal cramps" or "colicky", intermittent loose stools, diarrhoea, anorexia, and weight loss reported in >10% of patients [12].

An early syndrome

Develops within a few days or weeks of starting clofazimine and it may be due to a direct irritant effect of the drug. This syndrome was seen in patients receiving a high dosage, especially when the drug was given in a single dose, 300 mg daily, than when it was given in divided doses, 100 mg three times a day. The symptoms subsided once the drug had been reduced or discontinued [44].

A late syndrome

After some months or years on high dosage (more than 300 mg daily), with persistent diarrhoea, loss of weight, and abdominal pain.[12,45]

Serious side effects of clofazimine induced fatal enteropathy [45]

3 types of enteropathies

- Eosinophilic/allergic pattern
- Crohn's disease-like pattern with granulomas
- Clofazimine-induced crystal-storing histiocytosis

Crystal enteropathy developed due to several months of high-dose clofazimine >100 mg daily because of red crystal deposition in the small bowel lamina propria.

Other GIT adverse effect

intestinal obstruction, gastrointestinal bleeding, and splenic infarction [12].

Ocular

46% of patients receiving clofazimine treatment showed conjunctival deposition, 53% display crystal deposition in the cornea and 32% of patients present with crystals in their tears [46-48].

Qt prolongation and arrhythmia

Drug interaction

Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, fluoroquinolones, delamanid, azole drugs, and many others)

Contraindication

Hypersensitivity reaction

FDA category –C (Relatively contraindicated in pregnancy and lactation)

Monitoring – ECG, pregnancy, GI symptomology.

CONCLUSION

Due to its anti-inflammatory and antimicrobial properties potential for effective use in many dermatological diseases, either singly or as adjuvant therapy. The adverse effects particularly enteropathy should be given due consideration and precaution should be taken after starting the therapy.

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