CONTINUING MEDICAL EDUCATION

CLOFAZIMINE

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In the recent years there has been a renewed interest in the various aspects of clofazimine. Properties of clofazimine are being investigated in diverse clinical and experimental situations. This drug is basically a substituted iminophenazine dye which was synthesised by Vincent Barry and co workers in Dublin in 1954.[1] It is mainly used as antileprosy and antiinflammatory agent. It was first given to leprosy patients in Eastern Nigeria in 1962.[2]

There are almost nine chemical analogues of clofazimine, among which B 746 and B 4101 have better activity against certain drug susceptible and drug resistant strains of M. tuberculosis.[3]

Franzblau et al[5] have tested several analogues of clofazimine and found that pigmentation with lipophilicity and that lipophilicity is also associated with activity against *M. leprae*.[5] The current challenge is to devise a clofazimine analogue that is lipophilic enough to kill *M. leprae* but not so lipophilic as to cause hyperpigmentation.[6-8]

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Mechanism of action

Clofazimine is a widely used but a less understood drug, particularly for its mode of action.

Antibacterial action

Clofazimine binds to guanine residue of DNA, which are more abundant in bacteria than in mammalian cells,[4] but this does not exclusively explain its antibacterial effect. Clofazimine increases the activity of bacterial phospholipase A_2 and release of its enzymatic hydrolysis products, lysophospholipids which are toxic to mycobacteria and gram positive organisms.

Immunological actions

Clofazimine exerts its proinflammatory effects in neutrophils and monocytes by stimulation of myeloperoxide mediated iodination, phagocytosis and release of lysosomal enzymes. Krajewska et al[9] demonstrated that clofazimine stimulated oxygen consumption and superoxide generation by neutrophils. Anderson et al[10,11] found that clofazimine causes phospholipase A2 activation in neutrophils, resulting in increased release of lysophosphatidylcholine and arachidonic acid from neutrophil membrane. Clofazimine

auguments prostaglandin E2 production in normal neutrophils as well as neutrophils from chronic myelocytic leukemia and chronic granulomatous disease.[12-14]

Clofazimine also reduces sulphydryl content of mononuclear leukocytes and inhibits their mitogen induced transformation.[15]

An enhancement of inhibition of lymphocyte proliferation by cyclosporin A combined with clofazimine was observed in a study by Prinsloo et al.[16]

Absorption, Distribution and Excretion

Clofazimine is not homogenously distributed in the tissues and there is marked tissue accumulation. Because of this, determination of minimum inhibitory concentration for M. leprae is not possible.[17] In the mouse foot pad system the multiplication of *M. leprae* is inhibited by feeding 0.0001% to 0.001% clofozimine in the diet.[18] Bacterial killing begins after 50 days in patients on usual dosage of clofozimine and subsequently increased rates of bacterial killing are identified.[19]

Pharmacodynamics of the drug has been studied but gaps remain.[20,21] The drug is well absorbed from the GI tract particularly if it is suspended in oil and the drug particle size is under 5p. After absorption, the drug is preferentially deposited in certain cells and tissues, especially the liver via the portal system. In the serum, clofazimine is linked to lipoprotein carrier and is thus able to pass through cell wall membranes in solution. The level of the drug in the serum is not related in a linear fashion to the doses or frequency of administration. clofazimine has five-fold affinity for tissues,[20] and hence is concentrated in subcutaneous fat, liver, spleen, lungs, lymph nodes, suprarenals, etc. Lowest concentration is in the brain. Autopsy studies have confirmed these findings.[22] Though the peripheral nerves do not show typical coloration, measurable amounts of clofazimine are present in them. Balakrishnan and Seshadri[23] reported decreasing concentration of the drug in the skin of lepromatous patients after stoppage of therapy. Clofazimine was still detectable in skin and macrophages after 2 years of drug discontinuation. In the phagocytes of reticuloendothelial system and in lipid containing tissue the drug is seen as crystals of characteristic appearance.[24]

The half-life of clofazimine is at least 70 days in man.[25] The drug is cumulative. About 35%, on the average, of orally administered drug is excreted in the faeces.[21]

The drug is excreted in the bile after passage through liver.[25] A small amount, upto 1.08% is lost unchanged in the urine,[26] and smaller amounts in sweat, milk, sebum, tears and sputum. All body fluids may be tinted by typical reddish orange pigment.

Therapeutics

At present, clofazimine is most extensively used for the treatment of leprosy and ENL reaction. Its use in leprosy in India was probably reported for the first time in 1973.[27] Its usefulness in general protection against reactions is probably due to its immunosuppressive and anti inflammatory action along with antimicrobial cover.[28] Clofazimine does not show cross resistance with streptomycin, dapsone or rifampicin.[29] Several reports indicate that the overall antibacterial effect of clofazimine in

lepromatous leprosy is of the same order as that of dapsone.[30] It is an effective drug for ENL reaction, but certainly not as effective as corticosteroids, or thalidomide.[31] Combined treatment with clofazimine and corticosteroids controls the reaction more rapidly than either of the drug given alone. According to many observers clofazimine does not appear to be effective in the management of reversal reactions[32,33] for which prednisolone will be the drug of choice. Other workers have however found clofozimine useful in neuritis associated with reversal reactions[34] but it was more effective in combination with steroids.[35]

Combined therapy with clofazimine and dapsone is likely to prevent the emergence of dapsone resistance. Very few documented cases of true resistance to clofazimine have been reported.[36]

Apart from leprosy, clofazimine has been used in many other conditions. Some of the conditions are described below.

Atypical mycobacterial infection

Clofazimine inhibits the growth of atypical mycobacteria both in vivo and in vitro.[37-40] The most common indication for the use of clofazimine for atypical mycobacterial infections is part of the multiple drug therapy for disseminated *Mycobacterium avium intracellulare (MAI)* infections associated with AIDS.[41] Clofazimine is used in conjunction with isoniazid, rifampicin, clarithromycin, ethambutol and amikacin.[42,43] Clofazimine has been successfully used in the treatment of extensive *Mycobacterium marinum* infection in an infant[44] and in the treatment of *Mycobacterium hemophilum* and *Mycobacterium kansasii* infection in patients with AIDS.[45,46] Historically, clofazimine has been used in the treatment of Buruli ulcer as a single agent[47,48] but a recent study has shown clofazimine monotherapy to be ineffective.[49]

Vitiligo

Punshi[50] reported extremely good result in vitiligo obtaining repigmentation in 21 of his 30 patients. Clofazimine was thought to stimulate melanocyte system in vitiligo. Results were disappointing in the studies of Kumar and Kaur,[51] Handa and Ahmed[52] and Guha et al.[53]

Discoid lupus erythematosus

Krivanek et al[54] reported good to excellent response in 75% of their 10 DLE patients. Lo[55] recommended clofazimine as one of the modalities to treat DLE. It was not found effective by Jakes et al[56] and Kumar.[57]

Neutrophilic dermatosis

Clofazimine has been tried in pyoderma gangrenosum with variable success.[58,61] Clofazimine 300 to 400 mg daily, has induced remission of pyoderma gangrenosum in several patients whose disease had been resistant to systemic steroids, antibiotics and salazopyrin. These patients had pyoderma gangrenosum associated with ulcerative colitis or myelofibrosis or had no underlying disease. It is also reported to be of some benefit in Sweet's syndrome.[64]

Pustular psoriasis and acne are among the other conditions where clofazimine has been found to be effective.[63,65-67]

Herrero et al[68] noted remission of malakoplakia with clofazimine and trimethoprim sulfamethoxazole in a patient who was immunosuppressed after kidney trans-

plantation. Shehata and Salama[69] treated 76 patients of rhinoscleroma with clofazimine and obtained complete resolution in 38. Evans et al[70] found clofazimine to be highly effective against Leishmania major, both in vitro and in vivo. Clofazimine has also been found to be effective against Crohn's disease, facial granuloma and as a chemosensitizing agent against human lung cancer cell line.[71-74] In the series of Sussman et al[75] clofazimine induced complete remission in 5 of 11 patients of Melkersson-Rosenthal syndrome. Mensing[76] treated 10 patients each of necrobiosis lipoidica diabeticorum (NLD) and granuloma annulare (GA) with clofazimine and noted 60% response and 30% complete remission.

Presentation and dosage

Clofazimine is presented in micronised form suspended in an oily base in capsules of gelatin in 50 and 100 mg strengths. Clofazimine stays active for over 5 years if protected from heat and humidity.

Clofazimine can be administered daily or on alternate days. The dosage should be based on body weight but roughly the doses for adults is 50 mg daily or 100 mg on alternate days and for children 50 mg twice a week. Monthly loading dose of 300 mg is given in WHO multibacillary regimen for leprosy. In adults doses exceeding 200 mg/day should not normally be given for more than 3 months.

Toxicity

Clofazimine is generally well tolerated when given in a dose 50 mg daily.

Although it crosses the placental barrier no teratogenic or mutagenic effects have been demonstrated in animal studies or in humans. However the infant may be pigmented at birth. Abnormal pigmentation of the skin and dryness have been commonly reported. The initial redness which appears 1-4 weeks after treatment is due to accumulation of the drug. Reddish brown, mauve and violaceous brown pigmentation develops during the second and third months of treatment chiefly in the lesional area. Pigmentation of the skin has been observed in most of the patients and is more prominent on the exposed areas. Concentration of the drug decreased gradually over 2 years. Pigmentation is known to lighten gradually as early as 2 months after stopping treatment, but was noticeable in some patients even after 3 years.

Moore[77] reported dryness of the skin accompanied by itching in 25% of the patients and this was worse in winter. Shah[78] reported dryness of the skin in 50% of his vitiligo patients who had been given 100-300 mg per day of clofazimine for 6 months. Bharadwaj et al[79] reported low levels of vitamin A in the skin of patients on clofazimine which were thought to account for dryness of skin.

Gastrointestinal side effects have been reported to be common and troublesome especially with prolonged use of clofazimine. As 35% of the drug is excreted in faeces the predominance of GI symptoms and signs is not difficult to explain. Gastrointestinal tract may be affected directly by the local irritant effect of the drug and so the symptoms are dose related in early part of the treatment. Acute gastrointestinal symptoms are more common but they subside on reducing the dose or withdrawal of the drug. These symptoms are nausea, vomiting and diarrhoea. Severe diarrhoea and death have also been reported by Lal et al.[80]

The chronic gastrointestinal side effects or the late syndrome commences after some months or years after the treatment especially in patients having higher dosage. The symptoms of such late effect are persistent diarrhoea, weight loss and abdominal pain. Nine of the 84 patients of Ramu and Iyer[81] developed severe vomiting, diarrhoea, abdominal pain and hypokalaemia and 4 of them died. There was deposition of clofazimine crystals in the submucosa of small intestine and in the mesenteric lymph nodes in these cases. This may lead to death and may also explain persistence of severe abdominal symptoms even after stopping the drug. Eosinophilic enteritis developed in a patient who took 600 mg clofazimine daily for 3 years.[82] Bergeyck et al[83] reported persistent GI symptoms and diarrhoea with radiological evidence of small bowel constriction and circumscribed polypoidal area in a patient on long term high dosage (300 mg daily for 9 months)of clofazimine. Plock and Leiker[84] reported diarrhoea and pain some times colicky, in 7 of their 17 patients who have taken 100 - 600 mg of the drug for up to 5 years. However there are many large studies which refer to the safe nature of the drug. Absorption parameters were not affected in the patients studied by Kumar et al.[85] None of the patients of Handa and Ahmed[52] and Kumar et al[51] reported any GI side affects. Brown et al[86] found no GI side effect in their twelve year experience with 31 patients. Clofazimine has been rather safely and successfully used in the treatment of chronic inflammatory bowel disease.

Eight cases of clofazimine toxicity of the 8th cranial nerve were reported after 6 to 50 days of MDT. Of these, 2 were serious, 2 moderate and 4 slight. Dizziness, tinnitus and decreased hearing were symptoms which disappeared in 20 to 40 days of stopping the drug.[87]

Agranulocytosis caused by clofazimine has been described in a lepromatous patient.[88] After discharge from the hospital the patient used only DDS without any problem, but when clofazimine was restarted in dosage of 50 mg per day, he developed agranulocytosis and needed hopitalization again.

Generalised lymphadenopathy has been reported in patients on clofazimine.[89-99] In a few patients with multibacillary disease, pitting nontender and progressive pedal oedema has been observed on treatment with clofozimine.[91]

Conjunctival pigmentation, linear corneal streaks and macular pigmentation have been reported.[92] These changes are reversible and do not interfere with the vision and are due to deposition of clofazimine crystals. Bluish discolouration of the lens was reported by Karat.[93] Half of the patients of Moore[79] developed diminution of vision early in the course of treatment with clofazimine. Visual acuity, however was not affected in any of the 76 patients studied by Kaur et al[94] despite the presence of conjunctival and corneal pigmentation. Crystals in the tears started to appear after one year of therapy after ingestion of 20 gm of clofazimine in the study by Kaur et al.[94] Darkening of the color of urine and reddish brown discolouration of the sweat and sputum was noticed by almost all patients reported in various studies.

From the large scale studies available on clofazimine it can be said that clofazimine is free from serious side effects in the usual dosage and even in high dosage for short peri-

ods. Newer therapeutic indications other than leprosy are being investigated and the list of prospective usage is increasing.

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