CLOFAZIMINE: A REVIEW OF ITS USE IN LEPROSY AND *MYCOBACTERIUM AVIUM* COMPLEX INFECTION

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ABSTRACT: This article reviews the chemistry, pharmacology, spectrum of activity, pharmacokinetics, clinical efficacy in leprosy and *Mycobacterium avium* complex (MAC) infection, adverse effects, drug interactions, and special considerations of clofazimine. The drug is active in vivo against *M. leprae* and in vitro against MAC. In addition, it possesses antiinflammatory and immunosuppressive properties. Clinical studies support the efficacy of clofazimine as a part of multidrug therapy in treating leprosy. It also appears to reduce the incidence and severity of erythema nodosum leprosum reactions that often occur during the treatment of leprosy. Efficacy in treating MAC infection in patients with AIDS is not well documented, despite the use of clofazimine in combination with other agents. A few patients have responded symptomatically and by clearing their mycobacteremia, although there is no evidence that mortality is reduced. Clofazimine is well tolerated, at least when doses ≤100 mg/d are used. Adverse reactions include discoloration of the skin, self-limiting gastrointestinal intolerance, severe and life-threatening abdominal pain and organ damage due to clofazimine crystal deposition, and asymptomatic discoloration of the eye. Clofazimine should be considered for formulary inclusion.

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CLOFAZIMINE HAS BEEN USED in the treatment of leprosy (*Mycobacterium leprae*) since 1962. Because of the rarity of this disease in the US, clofazimine was available only as an orphan drug until recently. The current AIDS epidemic has led to the frequent occurrence of opportunistic infections. One of the most commonly encountered pathogens, found in 50 percent or more of AIDS patients at autopsy, is the *M. avium* complex (MAC).[1] Clofazimine frequently is used, in combination with other agents, in the treatment of MAC in AIDS patients. In this article, current knowledge regarding clofazimine is reviewed.

Chemistry

Clofazimine is a substituted iminophenazine bright red dye. Its chemical name is 3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-(isopropylimino)phenazine (Figure 1). Its molecular weight is 473.4. Commercially available capsules of clofazimine contain micronized drug suspended in an oil-wax base. Clofazimine is insoluble in water, sparingly soluble in ethanol, and readily soluble in benzene.

Pharmacology

MECHANISM OF ACTION AND RESISTANCE

The mechanism of action of clofazimine is not fully understood, but appears to involve binding to mycobacterial DNA, primarily at the guanine base.[2] This inhibits template function of the DNA strand, resulting in growth inhibition.

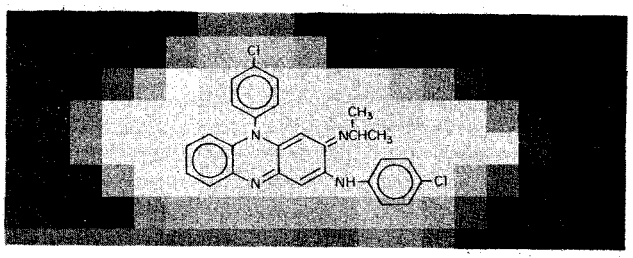

Figure 1. Graphic formula of clofazimine.

Clofazimine has been noted to possess both antiinflammatory and immunosuppressive effects.[3,4] This adds to its utility in treating leprosy by helping to control erythema nodosum leprosum (ENL) reactions, although corticosteroids frequently are required for severe cases (see *Clinical Efficacy* section). Detrimental effects due to the immunosuppressive properties of clofazimine, if any, in AIDS patients have not been investigated.

Any resistance of *M. leprae* to clofazimine is difficult to detect, because the bacillus cannot be grown in vitro. Instead, it must be evaluated in vivo using a mouse foot-pad model, in which mice are fed clofazimine 0.001–0.0001% in their diet. Clofazimine resistance has been reported in a single patient, but in vivo studies were unable to differentiate resistance from a normal variant wild strain.[5,6] Clofazimine-resistant MAC strains have not been reported.

SPECTRUM OF ACTIVITY

Because *M. leprae* cannot be grown in vitro, susceptibility testing and development of therapeutic alternatives have been hampered. Fortunately, *M. leprae* may be grown in vivo, and the development of a mouse foot-pad model has shown that clofazimine 0.001–0.0001% in the diet is able to inhibit growth of the organism.[4,7] Although mycobacterial killing apparently begins immediately, it cannot be detected in the mouse foot-pad model for about 50 days.[4,7] Determination of the activity of clofazimine is further confounded by the fact that *M. leprae* is an intracellular organism, and clofazimine is distributed unevenly in the body.

MAC may be grown in vitro, and minimum inhibitory concentrations (MIC) range from 0.1 to 10 μg/mL.[8,9] The majority of MICs are ≤2 μg/mL. Susceptibility of the isolate varies according to the test media in which it is grown. The lower the pH of the test media, the higher the MIC.[10] These investigators found that the MIC_{90} increased from 0.188 to 4.0 μg/mL as the pH of the broth was decreased from 6.8 to 5.0.

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Despite low MIC values for clofazimine against MAC, killing curve studies have failed to demonstrate a significant reduction in colony-forming units.[11] This is not surprising since minimum bactericidal concentrations (MBC) have been shown to be 32-fold or greater than the MIC.[10,11] In some cases, the MIC to MBC ratio has been as high as 1:256. Therefore, tolerance appears to occur with clofazimine.

Pharmacokinetics

The pharmacokinetic parameters of clofazimine are summarized in Table 1. Clofazimine is slowly and incompletely absorbed from the gastrointestinal (GI) tract following oral administration.[12-14] Bioavailability, when administered as a microcrystalline suspension in an oil-wax base (the commercially available preparation), has been reported to average 70 percent.[7] When it first was developed and administered as coarse crystals, bioavailability was only 20 percent. Absorption of clofazimine also has been reported to have an inverse relationship to dose. Mathur et al. found that bioavailability fell from 62.5 percent following 100 mg to 42.6 percent after 600 mg. However, there was little difference between 300, 400, and 600 mg in bioavailability.[14]

Following a single dose of 200 mg, the maximum serum concentration (C_{max}) averages 0.47 mg/L.[13] Administration with food increases the C_{max} by 28 percent (0.60 mg/L). The median time to reach maximum serum concentration is 12 hours in the fasting state, but shortened to 8 hours following administration with a meal. The area under the serum concentration versus time curve is also increased following administration with a meal, from 18 to 29.1 mg • hour/L.[13] Multiple-dose administration of 100 mg has been reported to produce a serum concentration of 0.7 mg/L two hours after administration, with the concentration increasing to 1.0 mg/L (300 mg) and 1.4 mg/L (400 mg) following higher doses.[15]

The volume of distribution of clofazimine has not been determined, probably because an intravenous form does not exist. Similarly, the type and extent of protein binding of clofazimine has not been studied. However, autopsies in several patients taking various doses of clofazimine for variable lengths of time have been performed, providing a great deal of information on tissue distribution (Table 2).[16,17] Because MAC infection occurs in many tissues and fluids, adequate distribution of clofazimine to these sites may be important in eliciting a therapeutic response. At autopsy, many tissues were noted to be abnormally stained yellow, orange, red, or brown. Because clofazimine is highly lipophilic, it distributes primarily into fatty tissues in the reticulo-endothelial system. Heavy deposits of crystals are often noted in the intestine, liver, and macrophages of the lymph nodes. Clofazimine apparently crosses the placenta and also distributes into breast milk.[4]

Clofazimine undergoes very little metabolism, with less than one percent recovered as metabolites in the urine in a 24-hour period.[12,15,18] Three urinary metabolites have been identified, but it is unknown whether they are pharmacologically active. Up to 50 percent of an administered dose has been recovered in the stool. Most likely, this represents unabsorbed drug and biliary excretion. A very small amount is eliminated in sebum and sweat.[7]

The elimination half-life of clofazimine has not been fully characterized in a carefully designed study. There appears to be an initial elimination phase with a half-life of seven to ten days.[12,13] This is followed by a much longer elimination period, probably resulting from release of the drug from fatty tissues and the reticulo-endothelial system, with a half-life of approximately 70 days. Following administration of 50 mg/d for eight days, a steady-state concentration is not achieved.[13] Computer simulation indicates that at least 30 days would be required to approach steady-state. These authors postulate that steady-state could be approximated more quickly by giving higher loading doses at the beginning of therapy.

The effect of various disease states on the pharmacokinetics of clofazimine have not been studied. Similarly, the effect of peritoneal and hemodialysis are unknown.

Table 1. Summary of the Available Pharmacokinetic Parameters of Clofazimine

Bioavailability	
coarse crystals	20%
microcrystalline suspension*	70%
Maximum serum concentration	
200 mg (fasting)	0.47μg/mL
200 mg (with food)	0.60μg/mL
100 mg (following multiple doses)	0.70μg/mL
Time to maximum serum concentration	
fasting	12 h
nonfasting	8 h
Elimination half-life	
initial phase†	7–10 d
extended phase‡	70 d

*The dosage form available commercially, which is a microcrystalline suspension in an oil-wax base.
†During the initial phase, clofazimine elimination from the serum and easily accessed peripheral compartments occurs.
‡During the extended phase, release and elimination of clofazimine from fatty tissues and the reticuloendothelial system is thought to occur.

Table 2. Tissue Concentrations of Clofazimine in Leprosy Patients at Autopsy

ORGAN	NUMBER OF PATIENTS	CONCENTRATION RANGE (mg/g)
Adrenal gland	1	2.0
Bile/gallbladder	2	2.0–3.6
Brain	4	none detected
Eye	1	1.1
Fat	4	2.1–5.3
Heart	3	0.3–1.5
Intestine	1	2.1
Kidney	4	0.04–1.4
Liver	4	0.18–3.2
Lung	4	0.17–1.4
Lymph nodes	3	1.0–3.3
Nerve	1	1.7
Pancreas	2	0.8
Skin	3	0.7–3.6
Spleen	3	0.6–1.9

Clinical Efficacy

A summary of studies evaluating the clinical efficacy of clofazimine in leprosy and MAC is shown in Table 3.

LEPROSY

Clofazimine has been approved by the Food and Drug Administration (FDA) for the treatment of lepromatous leprosy, including dapsone-resistant strains and disease complicated by ENL, or type 2, reactions. Prior to the first use

of clofazimine in 1962 for the treatment of leprosy, single drug therapy with dapsone was considered the regimen of choice. However, as dapsone resistance and treatment failures began to be reported, other drugs began to be evaluated in the 1970s. This eventually led to the recommendation by the World Health Organization, in 1982, that all lepromatous leprosy patients be treated with multidrug therapy.[27] Multidrug therapy consists of dapsone, rifampin and clofazimine.

Prior to the recommendation for multidrug therapy, Ahrens et al. compared dapsone and clofazimine as single agents in a multicenter, double-blind trial. A total of 94 patients were allocated to receive clofazimine 100 mg or dapsone 50 mg twice weekly and followed for 48 weeks. The incidence and rate of clinical, bacteriologic, and histopathologic response in the two groups was equivalent. Of importance, twice as many patients in the dapsone group experienced at least one ENL reaction.[19]

Multidrug therapy comprising dapsone, rifampin, and clofazimine has now been evaluated in several open, noncomparative trials. Tiwari et al. evaluated multidrug therapy in 58 institutionalized patients over a two-year period. Multibacillary leprosy was treated with a 14-day induction regimen of rifampin 600 mg/d, dapsone 100 mg/d, and clofazimine 100 mg/d. This was followed by a maintenance regimen of rifampin 600 mg once a month, dapsone 100 mg/d, and clofazimine 100 mg every other day plus 300 mg once monthly. Most patients required between 6 and 18 months to become bacteriologically negative on this regimen.[20]

Katoch et al. have reported their four-year follow-up experience with 56 patients treated with multidrug therapy that included clofazimine. Smears for acid-fast bacilli were negative within four years in the majority of patients. Skin lesions regressed in all patients during the first year. Bacillemia, which was present in 53 percent of patients at the start of therapy, had cleared in all patients by 2½ years. All patients completed 42 months of follow-up, but only 24 patients completed 48 months. The authors postulated that multidrug therapy may lead to long-term cures with relatively short durations of therapy.[21]

In a comparison of two different multidrug therapy regimens, Chattopadhyay et al. randomized patients to receive either clofazimine 100 mg every other day plus 300 mg monthly, or ethionamide 375 mg/d, in combination with rifampin 600 mg/d for three weeks followed by 600 mg/mo and dapsone 100 mg/d. Of 61 patients entering the study, 53 (31 receiving clofazimine) completed the two-year treatment period. Clinical improvement was based on a scoring system involving color, degree of infiltration, sensory loss, and involvement of peripheral nerves. Clinical improvement occurred more quickly in the first month in the ethionamide group; however, no difference was noted at later time points. More patients became bacteriologically negative (25.8 vs. 4.5 percent) in the clofazimine group by the end of the study. The incidence of ENL reactions was lower in the clofazimine arm of the study (30 vs. 50 percent). The results of this study favor clofazimine over ethionamide as the third drug in multidrug therapy.[22]

Because leprosy requires long-term therapy, patient compliance is a significant issue. It has led to the perceived need for monthly "supervised" doses of rifampin and clofazimine. Ellard et al. undertook a compliance study in 488 patients receiving multidrug therapy by monitoring urine samples to detect clofazimine and dapsone. They reported that more than 90 percent of their patients collected at least 90 percent of their medication from the clinic during the first two years of treatment. Urine tests indicated that 72 percent of the patients had taken their prescribed clofazimine and 78 percent took their dapsone.[28]

ENL reactions may complicate treatment of leprosy in up to 50 percent of patients during the first year.[4,7] The most common manifestations are fever, malaise, and tender, erythematous skin nodules. Severe reactions may be accompanied by joint swelling, orchitis, albuminuria, neuritis, iritis, epistaxis, and lymphadenopathy; hospitalization is often necessary in these cases. Corticosteroids and tha-

Table 3. Summary of Clinical Studies Evaluating the Efficacy of Clofazimine in the Treatment of Leprosy and MAC

REFERENCE	PATIENTS ENTERED (n)	PATIENTS COMPLETING (n)	COMPARATIVE DRUG/REGIMEN	CONCURRENT THERAPY	RESPONSE TO THERAPY
	Leprosy				
19	94	49	D	none	Clinical improvement 93% with clofazimine vs. 75% with dapsone; no difference in other measures; twice as many ENL reactions in dapsone group
20	58	58	none	Ri, D	Clinical response occurred in 46.5% of patients within 6 mo
21	56	24	none	Ri, D	Clinical response occurred in all patients within 1 y; bacillemia cleared in all patients within 30 mo
22	61	53	R, D, E	Ri, D	Clinical response occurred in 69.9% of clofazimine patients, vs. 73.3% in the other group; bacteriologic negativity was 25.8 vs. 4.5%, respectively
	MAC				
23	29		none	Rb, E, Et	No patient had an objective response to therapy; mycobacteremia persisted in 92%
24	13		none	Rb, A, others	Transient clinical improvement in 1 patient; transient negative blood cultures occurred in 7/13, but all relapsed
25	7		none	Rb, Et, I	Clinical improvement in 6 patients; transient negative blood cultures in 5, sustained in 1; 6 patients died within 1 y
26	4		none	Rb, I, Et	Clinical improvement occurred in all 4 patients; 2 patients died within 5 mo

A = amikacin; D = dapsone; E = ethionamide; Et = ethambutol; I = isoniazid; MAC = *Mycobacterium avium* complex; Rb = rifabutin; Ri = rifampin.

lidomide are the drugs of choice for treating ENL, but because of their serious adverse effects, clofazimine has been widely used. An initial dose of 300 mg/d is usually employed, tapering back as the patient improves. However, four to six weeks are often required to attain the full effect. The efficacy of clofazimine in treating ENL reactions probably is related to its antiinflammatory and antimycobacterial properties.

Clofazimine is more effective than dapsone in preventing ENL. In a comparative study, twice as many patients receiving dapsone developed ENL compared with clofazimine, a difference which was statistically significant.[19] Further proof for the efficacy of clofazimine comes from a report of 20 patients who experienced frequent ENL (average of once a month) while being treated with dapsone. Most of the patients (75 percent) already were being treated with steroids and chloroquine. Clofazimine was started at a dose of 300 mg/d, which eventually was tapered to 100 mg twice a week. After three months of treatment, only three patients continued to experience ENL, and the severity of their reactions was greatly reduced.[29]

Mishra and Girdhar reported that 22 of 30 patients with frequent ENL responded to clofazimine in doses up to 300 mg/d. In three of the eight nonresponders, lymphadenopathy developed after clofazimine was begun, so not all patients benefit from its use.[30] Similarly, clofazimine 50–100 mg/d as a part of multidrug therapy has been reported not to affect the incidence of ENL.[31] It is unknown whether this lack of response relates to the low dosage used, the intensive nature of multidrug therapy, or other as yet unidentified factors.

Reversal (type 1) reactions also may occur in leprosy patients. Existing lesions may worsen, and actual nerve damage may occur. Clofazimine does not appear to be beneficial in treating this condition, and in fact may worsen it. Corticosteroids are the drugs of choice for treating type 1 reactions.[4]

MAC IN AIDS PATIENTS

MAC was first recognized as a rare cause of slowly progressive pulmonary infection, usually in elderly men with underlying lung disease. With the advent of the current AIDS epidemic, MAC has been noted frequently, being present at autopsy in 50 percent or more of patients.[1] MAC has been cultured from nearly every tissue and fluid in the body, including the spleen, lymph nodes, liver, lung, adrenal gland, colon, bone marrow, and even the brain.[23] In contrast, MAC has primarily caused only pulmonary infection and lymphadenitis in non-AIDS patients.[1] The current problem is determining whether or not MAC is causing clinical infection, as opposed to colonization. Because AIDS patients with MAC often have concomitant infections, are receiving numerous drugs, and may have a malignancy, it is very difficult to determine MAC's contribution to fever, weight loss, organ dysfunction, malaise, and other typical signs of infection. This raises the issue of whether or not patients should be aggressively treated with combinations of powerful drugs.

Patients with disseminated MAC usually present with a long history of fever, malaise, night sweats, weight loss, diarrhea, and/or abdominal discomfort.[1,23,32] Their picture is often complicated by other opportunistic infections. Blood cultures are considered to be a practical and useful method for detecting MAC in AIDS patients.[1,32] Positive cultures of bone marrow, lymph nodes, liver, spleen, the upper GI tract, and other normally sterile tissues and fluids also are considered diagnostic of infection. However, positive cultures of sputum, urine, and stool, in the absence of other positive cultures, usually are considered to indicate colonization.[1,23,32]

Because of the aforementioned difficulties in diagnosing and assessing the response to therapy of MAC infection in AIDS patients, and because controlled clinical studies are lacking, an immunodeficient in vivo model (the beige mouse) has been developed to help bridge the gap between in vitro testing and clinical efficacy. Using this model, clofazimine 20 mg/kg po has been shown to be more effective than ethambutol and the investigational agent rifabutin (ansamycin). The combination of clofazimine and rifabutin was more effective than any single agent or other combination.[33] Serum concentrations produced by these regimens were not reported, so it is difficult to extrapolate these data to the treatment of human infection. In a follow-up study, the same investigators compared amikacin, clofazimine, and rifabutin, alone and in combination. Although amikacin alone was noted to be quite effective, the combination of clofazimine and amikacin was more active.[34] Endpoints considered in these two studies included mortality, reduction in the number of colony-forming units, and histopathologic examination of the tissues involved. The reader is referred to these articles for a more detailed account.

Hawkins et al. retrospectively reported their experience in treating 29 patients with MAC infection with the combination of clofazimine 300 mg/d, rifabutin, and either ethionamide or ethambutol. Many of these patients had multiple opportunistic infections. All isolates were susceptible in vitro to clofazimine at a concentration of 1 μg/mL. MAC was isolated from the blood of 90 percent of the patients, as well as many other sites. Despite combination drug therapy, all 29 patients had evidence of persistent infection. Of 26 patients with initially positive blood cultures, 24 had persistent mycobacteremia. At the time the report was written, 22 of the patients had died (76 percent); in the 17 who received an autopsy, MAC was isolated from at least one site. In addition, fever, malaise, anorexia, and weight loss persisted despite antimycobacterial therapy.[23]

Masur et al. treated 13 mycobacteremic patients with clofazimine 100 mg/d and rifabutin, as well as amikacin and other drugs as guided by susceptibility testing. Duration of therapy ranged from 33 to 530 days. Six of the patients had at least two consecutive negative blood cultures at some point during therapy. Two of these six patients relapsed and developed positive cultures again during therapy. In only one patient was there a clear correlation between conversion to negative cultures and clinically apparent improvement.[24]

Agins et al. have presented a more encouraging picture of MAC treatment. Seven patients with mycobacteremia were treated with clofazimine 100 mg/d in combination with rifabutin, isoniazid, and ethambutol. At least two consecutive negative blood cultures were noted in six patients. In addition, these six patients reported clinical improvement in their symptoms of fever, weight loss, and night sweats. However, all of the patients but one died within one year; the seventh died after 17 months.[25]

Bach has reported his experience in treating MAC infection in four AIDS patients, using the combination of clofaz-

imine, rifabutin, isoniazid, and ethambutol. However, only one of these patients had a positive blood culture prior to therapy, and follow-up cultures were not reported for any of the patients. Clinical improvement was noted in all four patients, although two of them died within five months. Follow-up had only occurred for three and five months in the other two patients.[26]

It is obvious from these reports that combination therapy, including clofazimine, has been largely ineffective in treating MAC infection in AIDS patients. Controlled, comparative trials are not available, a problem that may persist for some time. New regimens, containing amikacin and ciprofloxacin, are being recommended based on in vitro and in vivo test results.[32] In the meantime, combination therapy appears to provide symptomatic relief to some patients, so it seems reasonable to offer it to them once the potential risks and benefits have been explained.

Pediatric Considerations

The safety and efficacy of clofazimine in children under 12 years of age have not been established. However, clofazimine has been used in a small number of children.[4]

Adverse Effects

Most patients treated with clofazimine in a dose ≤100 mg/d tolerate it quite well. Higher doses, especially ≥300 mg/d, may cause severe adverse effects. The most common adverse reactions secondary to clofazimine affect the skin, GI tract, and eye (Table 4).[4,7,35]

Table 4. Commonly Reported Adverse Reactions Secondary to the Use of Clofazimine

Skin
pink to brown-black discoloration
discoloration of body fluids and secretions
ichthyosis and dry skin
rash, dermatitis, pruritus
Gastrointestinal Tract
early in therapy
anorexia
nausea
diarrhea
late in therapy
anorexia
nausea
vomiting
weight loss
abdominal pain
splenic infarction
eosinophilic enteritis
Eye
red-brown discoloration
clofazimine microcrystals
brown lines/streaks in cornea

SKIN

A pink to brownish-black discoloration of the skin is quite common, occurring in nearly all patients receiving the drug. Discoloration is thought to occur because clofazimine is a red dye. The skin usually becomes discolored during the first few weeks of therapy and the discoloration usually disappears within several months after clofazimine is stopped. Discoloration also has been present in neonates at birth if the mother has taken clofazimine during pregnancy. At autopsy, patients who have received clofazimine usually display a red-orange discoloration of many organs and tissues, especially the GI tract and fatty tissues.[16,17] Clofazimine is secreted in sweat, tears, sputum, and other body fluids, making it important to warn the patient to expect a red-brown discoloration.

Ichthyosis and dry skin are encountered in up to 75 percent of patients treated with clofazimine.[4,7,35] Application of oil, petrolatum, or a 25 percent urea emollient lotion can alleviate this problem.[4,36] Other rarely occurring adverse reactions involving the skin include rash, pruritus, and exfoliative dermatitis.[4,37]

GI TRACT

The most serious and limiting adverse effect of clofazimine involves the GI tract. There are two possible syndromes, one occurring early which is self-limited, the other occurring late, which is potentially fatal.[7] The early reaction consists of anorexia, nausea, or diarrhea and probably is due to a local irritant effect of the drug.[4,35] It responds promptly to reduced dosage or discontinuation of the drug. The late occurring reaction involves anorexia, nausea, vomiting, weight loss, and/or abdominal pain.[7,38,39] It usually occurs during long-term therapy with dosages >100 mg/d. Despite discontinuation of clofazimine, the patients may not improve, and a few patients have died. At laparotomy, large deposits of clofazimine crystals in association with congestion of the small bowel mucosa and mesenteric lymph node enlargement have been found.[39,40] Splenic infarction and eosinophilic enteritis have been associated with this syndrome rarely.[40-42]

THE EYE

Red-brown discoloration of the cornea, conjunctiva, and lacrimal fluid occurs frequently in patients receiving clofazimine. Slit-lamp examination often reveals clofazimine microcrystals.[43,44] In addition, small brownish lines or streaks in the cornea have been described during clofazimine therapy.[45,46] These lines disappear slowly following discontinuation of the drug. To date, clofazimine has not been reported to affect color vision or visual acuity.

MISCELLANEOUS

Clofazimine is not mutagenic[47] and has not been reported to be teratogenic.[4] When used in pregnant women, hyperpigmented skin has been noted in the neonate. In addition, a 20 percent neonatal death rate has been reported.[48] Further work has shown reduced estrogen concentrations in women receiving clofazimine.[49] Despite these concerns, clofazimine is quite useful in pregnant women with leprosy and ENL reactions; thalidomide is contraindicated and high-dose prolonged courses of corticosteroids are not desirable. Therefore, the benefits and risks of clofazimine in pregnancy must be carefully weighed in each patient.

Drug Interactions

In six male leprosy patients who received a single dose of rifampin 600 mg in conjunction with clofazimine (dose not specified), a statistically significant reduction in the rate of rifampin absorption and time to reach maximum serum concentration was noted.[50] Bioavailability was not affected, so this interaction is unlikely to be significant. In a mul-

tiple-dose study, clofazimine had no effect on rifampin pharmacokinetic parameters.[51]

Similarly, three multiple-dose studies have failed to detect any effect of clofazimine on dapsone pharmacokinetics in leprosy patients.[52-54] In contrast, isoniazid has a significant effect on clofazimine pharmacokinetics. In seven of ten leprosy patients receiving clofazimine 300 mg/d, concomitant isoniazid-reduced clofazimine tissue concentrations were measured by biopsy. In addition, serum clofazimine concentrations and urinary excretion were increased through this interaction. The authors postulated that isoniazid mobilized a tissue depot of clofazimine, resulting in more drug in the blood and less in the tissues.[54]

Summary

Clofazimine has been approved by the FDA for the treatment of leprosy. It is particularly useful in preventing or treating leprosy patients with frequent or severe ENL reactions. Because leprosy is rarely encountered in the US, this may not comprise its largest area of use here.

The current AIDS epidemic, in which MAC is frequently encountered, has provided a different role for clofazimine. Although the overall experience in treating MAC infection in AIDS patients with clofazimine combined with other agents has not been favorable, it is clear that some patients respond by clearing their mycobacteremia and becoming asymptomatic. Thus, it seems appropriate to make the drug available to these patients. Ongoing studies, using in vivo test systems, may produce a combination of drugs, including clofazimine, which is very active against this difficult infection. A great deal of work must yet be done to clarify this issue. Because of clofazimine's long elimination half-life and uneven tissue distribution pattern, alternative dosing strategies may be possible which maximize its therapeutic potential while minimizing adverse reactions.

Clofazimine should be added to formularies at institutions that are involved in the treatment of either leprosy or AIDS. It also should be available on an outpatient basis. Cost is not a major concern, as a 100-mg dose is approximately the same as a bedtime dose of a histamine H_2-receptor antagonist. There are no therapeutic equivalents to clofazimine, and it is particularly useful as a component of multidrug therapy.≃

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EXTRACTO

El artículo evalúa la química, farmacología, espectro de actividad, farmacocinética, efectividad clínica en el tratamiento de lepra y de infecciones causadas por *Mycobacterium avium* complex (MAC), efectos secundarios, y otras consideraciones sobre el uso de clofazimina.

El fármaco tiene actividad in vivo contra *M. leprae*, y en vitro contra *M. avium* complex. Además posee propiedades antiinflamatorias e immunosupresoras. La absorción de clofazimina a través del trayecto gastrointestinal es lenta e incompleta. Su eliminación es en gran medida en la forma intacta por la orina y en las heces fecales. Los estudios clínicos apoyan la efectividad de clofazimina como parte del régimen de múltiples medicamentos que se utilizan en el tratamiento de lepra. El fármaco también parece reducir la incidencia y severidad de la reacción de eritema nodosum leprosum que ocurre comúnmente en el tratemiento de esta condición. La efectividad en el tratamiento de MAC en pacientes con SIDA no está muy bien documentada. Algunos pacientes han demostrado una mejoría disminuyendo la sintomatología, al igual que se ha logrado erradicar la micobacteremia, pero no se ha alterado la mortalidad. Clofazimina ha sido bien tolerada en dosis de hasta 100 mg/d. Efectos adversos incluyen decoloración de la piel y de los ojos, intolerancia gastrointestinal, dolor abdominal severo, y daño a órganos secundarios a la deposición de cristales del fármaco. Aunque clofazimina se había utilizado en el tratamiento de lepra desde 1962, el número de estos casos eran limitados. La epidemia de SIDA ha llevado al uso frecuente del fármaco, ya que uno de los patógenos que más comúnmente causa infecciones oportunistas en esta condición es *M. avium* complex. Clofazimina es utilizada frecuentemente en combinación con otros agentes antiinfectivos para el tratamiento de esta condición en pacientes con SIDA. Se necesitan estudios comparativos controlados que evalúen el tratamiento de esta infección que es tan difícil de tratar.

WANDA MALDONADO

RESUME

Clofazimine est utilisé dans le traitement de la lèpre et des infections du complexe *Mycobactérium avium* (CMA) chez les patients atteints du SIDA. Cet article porte sur l'efficacité clinique du clofazimine dans ces deux indications. De plus, la chimie, la pharmacologie, le spectre d'action, la pharmacocinétique de ce médicament y sont revisés. Les effets secondaires, les interactions médicamenteuses et certaines considérations spéciales du clofazimine y sont également discutés. Clofazimine est actif in vivo contre le *M. leprae* et in vitro contre CMA. Par ailleurs, il possède des propriétés anti-inflammatoires et immunosupressives. Son absorption gastrointestinale est lente et incomplète. Clofazimine est éliminé principalement sous forme inchangée dans l'urine et les selles. Des études cliniques ont démontré son efficacité en association avec d'autres agents dans le traitement de la lèpre. Il semble aussi que clofazimine réduit l'incidence et la sévérité des réactions d'érythème noueux qui se produisent fréquemment lors du traitement de la lèpre. L'efficacité dans le traitement du CMA chez les patients atteints du SIDA n'est pas bien documentée, bien qu'il soit utilisé en combinaison avec d'autres agents dans le traitement de cette infection. Quelques patients ont eu une réponse symptômatique et une éradication de l'infection, quoiqu'il n'y ait pas d'évidence d'une diminution du taux de mortalité. Des études comparatives contrôlées n'ont pu démontrer l'efficacité du clofazimine dans le traitement de cette infection. Clofazimine est bien toléré du moins lorsque la posologie quotidienne n'excède pas 100 mg. Parmi les effets secondaires qui sont documentés, on note des décolorations de la peau, des intolérances gastrointestinales, des douleurs abdominales sévères, des dommages au niveau d'organes causés par des dépôts de cristaux, de même que des décolorations asymptomatiques au niveau des yeux. Clofazimine semble particulièrement intéressant lors de thérapie combinée. Son ajout au formulaire d'etablissements impliqués dans le traitement des patients souffrant de la lèpre ou du SIDA devrait être envisagé.

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