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The Antileprotic Action of Clofazimine (B663, G 30 320, Lamprene)[1, 2]

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In 1957 Barry *et al* (1) published a study on a series of phenazine compounds, including amongst others, B663 (G 30 320, Lamprene, clofazimine) which had been synthesized by them, giving evidence of a high level of antituberculous action. In 1958 Vischer *et al* (19) carried out a study of such phenazine compounds and their effects on experimental animals. In 1962 Chang (10) received B663 from Barry for checking into its efficacy in murine leprosy. Although this drug was originally intended for the treatment of tuberculosis, trials carried out simultaneously in Paris and Borstel did not produce the expected results. Barry and Cochrane then planned its trial in leprosy in Nigeria. First results were published by Browne and Hogerzeil (6) in 1962. The drug was used for 16 lepromatous and borderline leprosy patients who had received practically no previous treatment during the six preceding months. A clearly antileprotic action was demonstrated on clinical and bacteriologic evidence. A reddish coloring in certain areas of the skin (periorbital, palms and soles of feet) free of specific infiltration, was observed. On the other hand, a progressive hyperpigmentation occurred which was most marked in specific lesions, but sometimes also all over the body. This was not accompanied by any subjective symptom and there was evidence of substantial absorption of the drug. In the same year Browne and Hogerzeil (7) published a second report in which the number of patients had been increased to 28, of which one group received therapy for 12 months. The authors refer to the possibility of drug resistance, arising after 12 months, which motivated a third study (8), but that was not confirmed by Browne (4) in a report presented after three years of B663 therapy. Browne's report not only confirmed previous results but also noted an anti-inflammatory action of the drug, to the effect that the frequency of leprotic reactions was considerably lower than that observed during sulphone therapy. Brechet (2) in 1963, confirmed the therapeutic effects of B663 in five cases of leprosy observed in Angola. In one of these, an intense *erythema nodosum leprosum* (ENL) reaction had occurred. In 1964 Shepard and Chang (18) demonstrated that B663, given in a dosage of 0.01% added to the ration fed to mice was capable of stopping multiplication of *M. leprae* inoculated in the foot pads of the test animals—a fact confirmed in 1967 by Gaugas (12).

In 1965 Williams *et al* (22), submitting three patients from Mexico to a B663 trial, confirmed the antileprotic action of the drug and also its ENL suppressing effect.

In 1966 Pettit and Rees (15) in Malaya, confirmed the antileprotic action of B663 and in 1967, together with Ridley (16), they obtained identical results in a study of six cases which had not previously been treated.

In 1968 Waters (21) showed that the same therapeutic effect could be obtained by administering smaller doses than those used previously; that is, at a level of 100 mg twice a week.

In Brazil the first study on the subject was published by Silva *et al* (17) in 1969, confirming not only the specifically antileprotic action of this drug but also subsidence of reaction under its effect.

In 1970 Gatti *et al* in Argentina, reported good results with a daily dose of 100 mg administered to 35 patients suffering from various forms of leprosy.

As far as the reaction suppressing action is concerned, opinion varies. Browne (3, 5, 9)

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[2]Study carried out jointly with the Institute of Leprology and the Hospital of the Curupaity Colony, Rio de Janeiro, Brasil. Presented to the XIV International Congress of Dermatology, Venice, 22-27 May, 1972.

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suggested that B663 has an anti-inflammatory action capable of suppressing or hindering ENL. Pettit [14] opposed this theory stating that B663 at the rate of 100 mg administered daily, during 14 months, had no effect on ENL. On the other hand, in addition to earlier observations [4, 9, 17, 22], new studies such as those published by Hastings and Trautman [13] in Carville, USA, and Warren [20] in Hong Kong, report a definite anti-ENL action on the part of B663. In London just before the IX International Congress of Leprosy, a group of leprologists [11] from different countries discussed, at a round table, the results of B663 in the treatment of leprosy. The present report summarizes further therapeutic experiences with clofazimine in 20 advanced lepromatous patients.

MATERIALS AND METHODS

Twenty lepromatous patients at the Curupaity Hospital were treated with clofazimine.

Characteristics. There were 16 females and 4 males ranging in age from 15 to 69 years, predominantly adult, with half being in the range of 30-39 years. Nineteen were Brazilians and one Portuguese (12 Negroid and 8 Caucasoid). They had had leprosy from 1 to 28 years; 16 having had the infection for over 10 years. Five had not had previous leprosy treatment, whereas 15 had been treated with either sulfones alone or in combination with Ciba 1906, TBI, hydrazide or Tebessal for up to 30 years. Fourteen of these cases having been treated for over five years with negative results and the other also having shown negative results, all 15 were regarded as sulfone resistant.

Pretherapy examination. In addition to complete physical examinations the patients were subjected to evaluation of acid-fast bacilli by smears from nasal mucosa, skin and ear lobes. Additional determinations included: urine examination, hemogram, as well as blood sugar and blood nitrogen determinations.

Treatment. Thirteen patients were treated for two years and seven for one year. The initial dosage given to 13 patients consisted of two 100 mg capsules of clofazimine daily, for periods ranging from 1 to 14 months. The dosage was then reduced to 100 mg per day. Seven patients received 100 mg per day continuously. In general, patients received regular and continuous treatment. Thirteen patients received a total of from 40 gm to 99 gm of clofazimine during a period of one year and seven patients a total of 30 gm to 83 gm over a period of two years. Practically all patients received a minimum of 100 mg per day.

RESULTS

Nonspecific supplementary examinations.

Urine. Urine was examined at quarterly intervals (total examinations = 81, for the 20 patients involved). Results were normal, before and during therapy, except for one case. This case showed some pus cells, RBC and hyalin casts on occasion, but did not develop any significant difficulties or symptoms.

Glycemia and nitrogenemia. Each patient had at least two examinations, one before and one towards the end of his treatment. The majority had three or more examinations. No patient presented any abnormal result.

Hemogram. In the 110 hemograms made before and during treatment, on the average of five per patient, generally at three month intervals the following facts were observed.

a) Before treatment, 16 of the 20 patients showed signs of anemia, though generally of a discreet nature (lower limits; erythrocytes = 3.600.000, hemoglobin = 10.5). Of the 16 anemic patients, 12 showed improvement up to the point of normality at the end of the period of therapy, despite the fact that quite deliberately no anemia combatting treatment had been administered. The other anemic patients remained stationary.

b) Of the four patients who had not been anemic prior to treatment, one became anemic: erythrocytes = 4.480.000 and hemoglobin = 12.15 gm before, and 3.950.000 and 10.5 gm at the end of the treatment period.

c) No quantitative or qualitative alterations in leucocytes were observed except for very slight occasional deviations.

Side effects. In spite of monitoring the program as carefully as possible the only side effects which could possibly be associated with this therapy were related to skin and digestive tract.

Skin: 15 of the 20 patients complained more or less intensely of dry skin, which caused some of them to apply oil. A reddish

TABLE 1. *Effect of clofazimine on leprotic reaction.*

Frequency	Before treatment	After treatment
Very frequent	3 cases	0
Frequent	3 "	1 case
Rarely	5 "	1 "
None	9 "	18 "

TABLE 2. *Results of clofazimine therapy in 20 lepromatous patients.*

Duration of treatment (in years)	Previous treatment	Regression of cutaneous lesions				Total
		Complete	Marked	Discreet	None	
1	yes	0	2	1	0	3
	no	1	2	1	0	4
2	yes	1	9	2	0	12
	no	0	0	1	0	1
Total	—	2	13	5	0	20

pigmentation was observed in five and a dark pigmentation in nine patients. Eczematous eruption in one case was kept under control. In 12 cases ichthyotic skin was observed.

Digestive tract: 13 patients had complaints of gastroenteric nature (dyspeptic symptoms), although very slight and perfectly controllable by appropriate medication. One patient claimed constipation.

Leprotic reaction. The frequency of leprotic reaction is given in Table 1. The drug had a clearly preventive effect on the appearance of leprotic reactions. After beginning the therapy, their frequency dropped from 11 to 2 cases.

It is worthwhile noting that:

a) the two patients who presented ENL under clofazimine therapy had never undergone any kind of treatment before;

b) one patient had reacted prior to treatment but reaction frequency increased during the early stage of therapy, then decreased until there was total disappearance of reactions;

c) the other patient had had no reaction before treatment but afterwards, and in connection with tonsillitis, presented occasional reactions which were overcome with thalidomide, without need to interrupt the clofazimine treatment.

Clinical evaluation. All cases treated were of an advanced lepromatous nature. No change took place in the neurological lesions. Cutaneous lesions, however, though quite profuse, improved in the course of both one and two years of treatment. Table 2 presents the main data concerning the clinical results of treatment.

Of the 15 sulfone resisting patients, 3 were given clofazimine for one year and 12 for two years. Of these, the regression of the lesions was complete in 1, marked in 11 and discreet in 3 cases. Of the 15 patients who had not received any previous treatment, 11 had complete, 2 marked and 2 moderate regression of lesions. Of the 13 cases who had received treatment for two years, 1 had complete, 9 marked and 3 moderate regressions. Of the 7 patients who had been treated for one year, 1 had complete, 4 marked and 2 moderate regressions.

Bacteriologic evaluation. Bacterioscopic examinations were carried out before therapy and at three month intervals during the course of therapy. Each consisted of six smears (two from the skin, two from the ear lobe and two from nasal mucosa). The results are given in Table 3.

The Granularity Index is the result of averages obtained from these examinations. After treatment there remained ten positive

TABLE 3. *Bacterioscopic tests on 20 patients treated with clofazimine.*

Treatment	Nose		Ear lobe		Skin	
	Positive	Negative	Positive	Negative	Positive	Negative
Before	17	3	20	0	20	0
After	13	7	9	11	9	11

TABLE 4. *Granularity Index of patients treated with clofazimine.*

Treatment	Granularity Index
Before	6.5
After	8.1

cases; the findings relate only to these respective ten cases. The average results are noted in Table 4.

Histopathologic findings. Histopathologic examinations were performed before, during and after treatment, yielding three biopsies per patient. Treatment resulted in a reduction of leprotic infiltration and considerably decreased number of bacilli. Granular bacillary forms and granulations prevailed over solid forms.

In no case was there complete disappearance of Virchow cells. These cells increased in size and showed marked intracytoplasmic lipid accumulation but became practically free of bacilli. Of these 20 cases, histologically evaluated as lepromatous leprosy prior to clofazimine therapy, eight became lepromatous-regressive. In some cases we found signs of brownish pigmentation in both dermis and epidermis.

DISCUSSION

We have intentionally selected a number of advanced lepromatous (L3) cases of longstanding, in order to check on the antileprotic action of this new drug. Fifteen of these cases had submitted to sulfone therapy a few years before, based either exclusively on sulfone or on a combination with other drugs. In this manner we succeeded in lending more weight to the favorable results which were obtained. Furthermore, we did not take corrective measures with regard to anemia of patients in the initial stages of therapy, because it was our aim to remain as close as possible to the actual sanitary conditions of the population. This permitted the conclusion that even under conditions as observed in Brazil, clofazimine therapy caused no inconvenience at all; quite the contrary, the majority of anemic patients improved their erythrocyte counts and hemoglobin levels. This fact may eventually be explained in other terms.

As to leukocyte count, no change took place. There was no alteration in the health status of the patients as far as could be observed during clinical and biochemical examinations, except to the minor "side effects" referred above. Patients accepted the pigmentation, so this does not seem to represent an impediment to the use of the drug; it tended to disappear when treatment was interrupted. We call attention, however, to the ichthyotic aspect and signs of parching which appeared very frequently during treatment. Conceivably one could be led into thinking that the ichthyotic state was a consequence of the edematous decrease of infiltration in patients as a consequence of the improvement obtained with clofazimine therapy. However, we do not accept this explanation for two reasons: 1) the ichthyotic condition persisted even after various months of reduced infiltration; 2) its presence was found even in areas of the cutis where, clinically speaking, no lesions had occurred. Consequently, we believe that there must be another explanation for the appearance of the ichthyotic condition following treatment of clofazimine.

Therapeutic results were considered good, in view of the clinical improvement of all

patients. Results observed on 15 of 20 patients were very good, while the remaining five patients gave signs of a more discreet improvement. We did not analyze by themselves the groups of one or two years of therapy, because the results were practically identical and the sampling was a small one.

Anyway, it is necessary to say that all the 15 sulfone-resisting cases presented good results. With regards to 12 of these, results were considered very good. The antileprotic activity of the drug becomes evident, as seen in the light of bacterioscopic results, in that 50% became negative at the end of the treatment and in the other 50% who remained positive, the Granulation Index showed a marked improvement.

Histopathologic results tend to confirm the antileprotic action because of 20 cases of lepromatous lesions (results of the first biopsy), eight became cases of regressive lepromatous infiltration. The fact that out of the 20 patients, 11 showed leprotic reaction prior to clofazimine therapy and that this number was reduced to two in the early stage of therapy, as well as the fact that with the continuation of treatment, leprotic reactions disappeared, justifies our belief that the drug probably develops an impeditive effect on the appearance of leprotic reactions.

SUMMARY

Therapeutic results obtained with clofazimine in 20 patients in advanced stages of long-standing lepromatous leprosy, 15 of whom were sulfone-resisting cases, are presented.

Based on the clinical results (all patients improved; 15 of them in an outstanding manner), the bacteriological findings (50% negative, 50% clearly improved Morphologic Index) and histopathologic results (8 out of 20 patients suffering from lepromatous infiltration in the initial stage showed repressive lepromatous infiltration towards the end of therapy), it was concluded that:

1. Clofazimine has a clearly discernible specific therapeutic effect on leprosy.
2. The drug is effective in cases of sulfone-resistant lepromatous leprosy and consequently must be considered as a possible choice of treatment in such cases.
3. Clofazimine therapy does not induce leprotic reactions at the same rate of frequency as observed under sulfone therapy.
4. The drug's side effects are negligible (pigmentation, ichthyotic condition and slight gastrointestinal affections) and should not be regarded as contraindications to its use.

RESUMEN

Se presentan los resultados terapéuticos obtenidos con clofazimina en 20 pacientes en estado avanzado de lepra lepromatosa de larga evolución, 15 de los cuales eran casos sulfono-resistentes.

Basándonos en los resultados clínicos (todos los pacientes mejoraron; 15 de ellos en forma notable), los hallazgos bacteriológicos (50% se hicieron negativos, en 50% el Indice Morfológico mejoró notoriamente) y resultados histopatológicos (8 de 20 pacientes que mostraban infiltrado lepromatoso en las etapas iniciales, mostraron infiltración lepromatosa regresiva en las últimas etapas de la terapéutica), se concluye que:

1. La clofazimina tiene un efecto terapéutico claramente discernible sobre la lepra.
2. La droga es efectiva en casos de lepra lepromatosa sulfono-resistente y, en consecuencia, debe ser considerada como un tratamiento posible en esos casos.
3. La terapia con clofazimina no induce reacciones leprosas con la misma frecuencia que se producen con terapia a base de sulfona.
4. Los efectos secundarios de la droga son de poca importancia (pigmentación, condición ictiótica y ligeras molestias gastro-intestinales) y no deben ser considerados como contraindicaciones para su empleo.

RÉSUMÉ

On présente ici les résultats thérapeutiques obtenus par la clofazine chez 20 malades souffrant de stades avancés d'une lèpre lépromateuse de longue durée, dont 15 étaient résistants au sulfone.

On a étudié les résultats cliniques: tous les malades ont été améliorés et 15 d'entre eux d'une manière spectaculaire. On a étudié également les résultats bactériologiques: 50 pour cent devenus négatifs, 50 pour cent avec un index morphologique nettement amélioré. Quant aux résultats histopathologiques, 8 parmi les 20 malades souffrant d'une infiltration lépromateuse au stade initial, ont montré une régression de cette infiltration a la fin du traitement. De ces observations, on conclut:

1. La clofazimine est dotée d'un effet thérapeutique spécifique évident dans la lèpre.
2. Le médicament est actif dans des cas de lèpre lépromateuse résistant aux sulfones, et pourra dès lors être considéré comme un choix thérapeutique possible dans de tels cas.

3. La thérapeutique par la clofazimine n'entraine pas de réactions lépreuses avec la même fréquence que celle observée lors de la thérapeutique par les sulfones.
4. Les effets secondaires des médicaments sont négligeables (pigmentation, condition ichtyotique, et légers troubles gastro-intestinaux). Ces effets ne devraient pas être considérés comme des contre-indications à son emploi.

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