# The Control of Neuritis in Leprosy with Clofazimine <sup>1</sup> Roy E. Pfaltzgraff<sup>2</sup>

The aim of this study is to evaluate the usefulness of clofazimine in controlling the neuritic complications of infection with M. *leprae*. Previously reported studies of the use of clofazimine have utilized lepromatous patients, and only briefly refer to its value in controlling neuritis (1, 2, 3, 4, 5, 6, 7). The patients included in this trial are all in the tuberculoid and borderline portions of the spectrum.

Initially our intention was to make this a controlled study and to place representative patients on clofazimine with and without additional corticosteroids, along with comparable patients on dapsone or thiambutosine, also with and without corticosteroids. However, it was soon evident that such a study would have insurmountable technical difficulties. More importantly we saw that this would result in patients developing irreversible neurologic complications and would be morally indefensible.

The most important problems of leprosy relate to its neurological component, and in Africa some 40% to 60% of patients need therapeutic prevention of the permanent neural sequelae, and this is usually not attained with conventional therapy. This refers particularly to the patients in the TT and BT portions of the spectrum, where in many instances nerve involvement can be rapidly irreversible, and can be aggravated by conventional treatment with dapsone. The combination of corticosteroids with either dapsone or thiambutosine is not always effective in controlling the inflammatory response in nerves and also occasionally leads to steroid dependency and reversal reaction, either of which can readily lead to serious complications.

From preliminary trials of the use of clofazimine and the reports of others (<sup>5, 6, 8</sup>), it appeared that this drug would help to halt the progress of neural involvement,

and if clofazimine were combined with the judicious use of corticosteroids it might be possible to anticipate some return to more normal function, and at the same time avoid the hazards of prolonged steroid therapy. Thus it was thought worthwhile to seek a treatment regime which would most effectively halt and possibly reverse neural involvement in leprosy.

# MATERIALS AND METHODS

Selection of patients. Fifty-one patients were selected for this trial because they had neuritic manifestations of leprosy; such as enlargement of peripheral nerve trunks, pain and tenderness in these nerves, and sensory, motor and/or autonomic deficits. All the patients in the trial had nerve enlargement in at least one of the common sites of involvement. All but one patient had significant peripheral sensory loss, and 34 had motor involvement at the time they were entered into the trial.

An attempt was made to grade the three parameters of nerve involvement so as to determine the extent of damage prior to and following therapy based upon 1) nerve enlargement, 2) sensory, and 3) motor loss. These were graded as follows: 1+, mild; 2+, moderate; 3+, severe; and 4+, maximal. In motor involvement grades 1+, 2+ and 3+ evaluate weakness alone; only grade 4+ includes muscle atrophy.

It is recognized that it is difficult to objectively evaluate these criteria accurately, but they give a rough estimate of the degree of change shown by the patients after six months of therapy. Of the fifty-one patients in this study, only three could be carried to its completion on therapy other than clofazimine, and 37 of the remaining 48 had had treatment with varying combinations of antileprosy therapy with corticosteroids with a poor response before they were included in the trial.

Forty-one of these patients were male and ten female, with ages ranging from 11 to 50 years. The patients were clinically

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(and where available, histologically) classified; there being nine patients that were TT type, nine macular BT, ten infiltrated BT, four BB, and nineteen BL.

**Procedure.** Initially in the trial, five patients who had not had previous treatment were given clofazimine alone, but it was apparent after ten days to two weeks that this was inadequate to provide optimum relief of neuritis, and only three could be continued without any corticosteroid at all. Thereafter, all patients were given steroids when indicated for rapid relief of neuritic signs and symptoms.

Since the proper therapeutic regime for the administration of clofazimine in neuritis had not been established, various dosages were used and altered depending on the patient's response. Where improvement was adequate and neural complications appeared to be decreasing, the dose was reduced. Where there was inadequate response the dose was increased. Likewise, no established regime for the use of corticosteroids was available, so the same trial and error method was used. It was apparent that the steroid was essential for its prompt effect in conjunction with, or followed by clofazimine. Usually by the time the pigmentation of clofazimine became evident, the corticosteroid could be reduced and often soon stopped. Of this group of 51 patients, 48 received steroid to supplement antileprosy therapy. Three had none, and in retrospect, it appeared that it was indicated in two of them.

Over half of these patients began with a "loading" dose of clofazimine which was usually 300 mg/day for two to four weeks, before the dose was reduced to 100-200 mg per day, and continued at that level as long as neuritis appeared to be active. The time required for this varied a great deal, from 0.5 month to 36 months.

There was a wide variation in dose and duration of corticosteroid administration required. Most patients were given an initial dose of 40 mg prednisone daily, although in a few instances 80 mg was given to begin with. After four to five days this was halved. Thereafter, stepwise reduction at weekly intervals to 10 mg per day was used and terminated with 10 mg on alternate

					-	NERVE IN	VOLVEME	LU			
Type of	No.	Thick	cening	Sen	sory	Mo	tor	Tc	otal	Differ-	Percent
leprosy	pts.	pre-Rx	post-Rx	pre-Rx	post-Rx	pre-Rx	post-Rx	pre-Rx	post-Rx	ence	improved
TT	6	30	9	27	15	17	7	74	28	46	62
Mac BT	6	26	6	27	80	17	ъ	70	22	48	69
Inf BT	10	31	8	35	13	26	9	92	27	65	11
BB	4	11	c1	11	v	7	1-	29	14	15	52
BL	19	65	19	99	. 35	40	29	171	83	88	52
Totals	51	163	44	166	76	107	54	436	174	262	60
Difference % improved			19 73	συ	0.4	מנסנ	3	6	62 80		

days for two weeks or more. Reduction of dose was always based upon absence of pain and reduction in size of nerves.

## RESULTS

Clinical evaluation. Six months after beginning the use of clofazimine the results were evaluated using the same parameters of nerve enlargement, anesthesia and paralysis. The results are summarized in Table 1 where the patients with each type of leprosy are grouped together, and the numerical gradings of severity of involvement on the grade of 1+ to 4+ are added together for all the patients in each group, prior to and after therapy. The involvement observed is then added for each type of leprosy and for each of the three parameters of involvement, and they are finally expressed as a percentage of improvement occurring during six months of treatment. The most marked improvement occurred in the infiltrated BT group, but the level of improvement for macular BT is not significantly different, there being about 70% improvement in both types. The next in degree of improvement is seen in TT at 62%, and for BB and BL leprosy it averaged 52%. In comparing the parameters of nerve involvement, the most evident change was seen in thickening, with 73% improvement. Changes in sensory and motor involvement were essentially equal, being 54% and 50% respectively.

The number of patients on therapy other than clofazimine is insufficient to draw any relative conclusions. However, it is of great . significance that 37 of the group had previous therapy with other drugs, in most instances combined with corticosteroids. They did not improve, and some showed a deterioration in nerve function. When clofazimine and a corticoid were begun together, in all instances but two, prompt improvement was noted. One of the two that did not improve was taking dapsone without our knowledge, and the other had had long-standing disease and two years of prior therapy with dapsone, so that probably the nerve inflammation was no longer active.

Seven patients who had been doing well on dapsone or thiambutosine plus steroids were at the stage where it was essential to stop the use of the corticosteroids. When this was done an acute neuritis was precipitated making it necessary to change to clofazimine to prevent irreversible damage to nerves.

When clofazimine was used without corticosteroids, the improvement of neuritis was better than with any other leprosy drug used alone; but was not as effective as a combination of dapsone or thiambutosine together with a corticoid. Many patients on conventional antileprosy therapy do well, but the significant group is that composed of those who do not improve satisfactorily on dapsone or thiambutosine, but who show marked improvement in their neuritis when given clofazimine in conjunction with corticosteroids, despite the fact that corticosteroids were not effective in conjunction with the previous therapy. When dapsone had been used for less than a year before starting clofazimine, plus steroids, the response was still good, but if dapsone had been administered for more than a year, the level of improvement dropped 20%.

In grading the severity of neuritis by the amount of nerve thickening, plus pain and tenderness, the average patient initially had about 3+ or 75% involvement, there being no significant variation by type of disease. The degree of peripheral sensory loss was also about 3+. Motor involvement, however, was only about 2+ or 50%. All except two patients had more than 20% improvement, and 37 (74%) of patients had 50% or more improvement. In only one person did the extent of involvement remain stationary, and there was deterioration in only one, showing a slight increase in anesthesia of one limb. This was the patient that was getting dapsone inadvertently.

A study of the duration of administration of clofazimine, from two weeks, the shortest, to thirty-six months and continuing at the time of writing, reveals no correlation between the length of treatment course and the therapeutic response. It seems that a higher dose produces a more rapid improvement. Clofazimine was stopped when it appeared that an optimum response had been obtained. Then the patients were usually treated with dapsone, or in a few instances with thiambutosine.

Invariably, when clofazimine was begun in a patient previously on other therapy, it was necessary to temporarily increase the dosage of corticosteroid in order to prevent an exacerbation of reaction.

A puzzling finding is that in three patients, after a prolonged intensive course of clofazimine, there was an increase of neuritis. This was never severe nor did it involve an increase of sensory or motor loss. It consisted simply in the patient complaining of a return of nerve pains. One of these patients was found to be getting dapsone as well as clofazimine, and this could explain his symptoms; whereas in the other two no suitable explanation was found. On stopping clofazimine for a time the pain was relieved and later the drug was again given.

At one time, due to a temporary lack of supply, it was necessary to stop giving clofazimine. Three patients promptly complained of increased neural symptoms which subsided when the drug again became available. In seven patients an attempt was made to add dapsone to clofazimine therapy, or to switch to dapsone, This induced an increase of signs and symptoms, and in two patients there was a sudden development of bilateral foot drop which returned to normal on stopping dapsone and temporarily increasing the dose of steroids with the clofazimine.

Six of the 48 patients in this trial who were given clofazimine only attained improvement to 25% or less by the system of grading used. In these six, it was seen that there were three factors that could well explain the poor responses. All six patients had prolonged treatment with dapsone. In five of them, symptoms had been present for a long time before treatment was begun, and in four no, or inadequate, corticosteroids were used to control reactions. In spite of the poor results, in every instance there was still improvement in the general condition in a type of leprosy inherently difficult to manage.

Histopathology. Biopsies of skin and a branch of the radial cutaneous nerve were taken from 23 of these patients. Due to incomplete records and loss of specimens in transit, only eleven provide complete data before and after six months of therapy. A summary of the clinical and histopathologic data on these eleven patients (eight treated with clofazimine, one with dapsone and two with thiambutosine) reveal no findings that can be considered significant relative to the different therapies. Suggestive is the fact that the single patient on dapsone had only fair clinical response and with only moderate return of nerve function. Histologically this patient showed marked improvement in the skin lesions, but fibrous replacement of neural tissues.

There is close correlation between the level of improvement in the clinical condition and the degree of clearing of granulomas in skin and nerves. In all instances the nerves did not show as rapid an immunologic response as did the skin, and it also appeared to be a more severe involvement. Perhaps most importantly, after six months of treatment the nerve changes did not improve as well as did the skin lesions.

#### DISCUSSION

The management of the complications of nonlepromatous leprosy with clofazimine have not previously been reported in any detail. Tolentino (5) states that clofazimine is probably not significantly better than dapsone as an antileprotic drug when it is possible to use dapsone without aggravation of reaction. He found that erythema nodosum leprosum and neuritis occurred twice as frequently with dapsone as with clofazimine, and that the reactions were more severe. Initially we attempted to evaluate the effects of clofazimine alone, but soon found that the improvement in neuritis was too slow and that patients would likely develop permanent nerve damage before the inflammatory process was controlled, and so we felt it essential in most instances to add corticosteroids. Leprosy is one of the few diseases where antiinflammatory action of the corticosteroids is invaluable, since they can control the hyperactive cell-mediated immune response of hypersensitivity, while at the same time specific treatment can be directed against the etiological agent. Corticosteroids alone,

however, are inadequate in controlling reactional states in leprosy because without antileprosy therapy they will allow increased bacillary multiplication, and possibly a shift toward the lepromatous side of the spectrum of disease.

Although dapsone is very effective in killing M. leprae, in some cases it aggravates reactional states and when an attempt is made to control these with corticosteroids the patient's resistance may decrease so that there is a shift of the type of disease toward lepromatous, and bacilli may also develop resistance to dapsone therapy. In the patients here studied, as well as some 150 others, where reactions prevented effective use of dapsone, antileprosy treatment could be continued with clofazimine. Also in all instances of steroid dependancy, it was possible to stop their use after beginning clofazimine (5), while the Morphological Index was reduced at least as rapidly as with dapsone treatment.

It is essential to accept the concept that there is no "routine course" in the use of either clofazimine or corticosteroids. For patients with neuritis that threatens permanent damage, both should be used initially in high doses, and the corticoid stopped as soon as possible. The clofazimine dose also can be reduced depending upon the response of the patient, down to 100 mg three times weekly. When improvement is optimum and there is no longer pain or tenderness of nerves, clofazimine can be stopped and therapy continued with dapsone. In some patients when dapsone is tried there will be an increase in neuritis and it becomes necessary to use clofazimine again for a few months. Eventually it will be possible to use dapsone without inciting a reaction. There seems to be no advantage gained in combining dapsone or thiambutosine with clofazimine therapy.

It is important to note that 23 of these patients had what was considered an adequate trial of dapsone, thiambutosine, or both, plus corticosteroids and that they had not responded well. Probably both the duration of disease and previous therapy are of some significance in the response of patients (see Fig. 1). It is evident that if disease is present for a sufficiently long time reactive phases will ultimately not recur, but the time lapsing before reactions cease is variable and unpredictable. Probably after quiescence, the nerves having been seriously damaged, no return of function can be expected. The same results prevail where antileprosy treatment has resolved the reaction. Nerve damage remains unchanged and no improvement can



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be expected no matter what therapy is used.

The finding that nerve lesions are more severe and lag behind the rate of improvement of skin involvement is significant. We should not base therapy upon findings in skin biopsies since nerve pathologic changes are more severe, and it is not possible to histologically examine sections of larger nerves. Rather, two factors should be considered in treatment. Conservative use of those agents which aggravate reaction, and suppression of the reaction with antiinflammatory drugs including corticosteroids and clofazimine where indicated, stands first in the prevention of nerve damage. Secondly, where there is any evidence of nerve involvement regardless of the appearance of skin lesions, there should be no reluctance in temporarily stopping antileprosy treatment.

In studying the varying responses in the types of disease, some reasons for these differences become evident. In TT the response in nerves is so violent that it probably destroys nerves rapidly and the potential for return to normal is slight if the reaction persists even for a short time. In BT the onset of paralysis is not quite so rapid and there is time for the patient to obtain treatment since fibrosis is slower to set in and the changes remain reversible for some time. In BB and BL the process is so slow and insidious that the patient may not seek help while it is still reversible, but improvement is possible for quite a long time.

Thickening of nerves occurs because of cellular infiltration and edema and the potential for reversal is good. In fact, until fibrosis occurs we can expect continued improvement. The return of function to nerve fibers depends on the integrity of the axon, and if its continuity is destroyed, repair is difficult or impossible. Thus, for return of function a reduction in inflammation is essential at the stage of neuropraxia. If treatment reducing infiltration and edema is delayed, the potential for return of function is slight.

It is quite evident that this investigation is as much a trial of the efficacy of corticosteroids in the management of the neuritis of leprosy, as it is a trial of the value of clofazimine. It is, however, clear that the two drugs are complementary, and that the corticosteroids could not be utilized to their fullest extent without using clofazimine at the same time. The value of clofazimine in suppressing reactions, especially neuritis, is greatly potentiated by corticosteroids. No other antileprosy drug known can be continued in all instances even with supplemental corticosteroids and attain a good control of reactional episodes. To date, and after treating many more patients than those here cited with the combination of clofazimine and corticoids, we have never seen a patient who did not respond with a cessation of reaction and neuritis, as well as concomitant resolution of their disease. With clofazimine the initial course of corticosteroids can be terminated in an average of four to six weeks as neuritis subsides.

There are no significant complications with the use of clofazimine. None of our patients have complained of the increased darkening of the skin. Other side effects have all been of minor consequence, such as minimal acne, diarrhea and abdominal pain in a few instances, and rarely dryness and itching of the skin. In no instances was it necessary to stop treatment for any of these reasons.

### SUMMARY

The effect of clofazimine in controlling the neuritic complications of leprosy was studied, comparing it to the results commonly attained with dapsone or thiambutosine. The study included the use of corticosteroids where indicated. Thirty-seven patients were treated with either dapsone or with thiambutosine, or both, and when neuritis did not respond, were given clofazimine instead. In all instances there was improvement. The combination of clofazimine and corticosteroids is in every instance the ideal regime for controlling neuritic complications and a striking reversal of these manifestations can be expected.

#### RESUMEN

Se estudió el efecto de la clofazimina para controlar las complicaciones neuríticas de la lepra, comparándolo con los resultados obtenidos corrientemente con dapsona o con tiambutosina. El estudio incluyó el uso de corticosteroides en los casos en que estaban indicados. Se trataron treinta y siete pacientes con dapsona, con tiambutosina o con ambas drogas y, cuando las neuritis no respondieron, las drogas fueron reemplazadas por la administración de clofazimina. En todos los casos hubo mejoría. La combinación de clofazimina y corticosteroides constituye el régimen ideal en cada caso para controlar las complicaciones neuríticas y puede esperarse una notable mejoría de estas manifestaciones.

#### RÉSUMÉ

On a étudié l'action de la clofazimine dans les complications névritiques de la lèpre, en comparant l'effet de ce produit aux résultats habituellement obtenus avec la dapsone ou avec la thiambutosine. Cette étude a également fait appel à l'utilisation de corticostéroïdes, lorsque celle-ci était indiquée. Le nombre de malades traités soit par la dapsone, soit par la thiambutosine, soit encore par les deux médicaments, s'est élevé à trente-sept; lorsque qu'aucun effet n'a été noté sur la névrite, les produits ont été remplacés par la clofazimine. Dans tous les cas on a constaté une amélioration. La combinaison de clofazimine et de corticostéroïdes a toujours constitué la traitement idéal pour contrôler les complications névritiques. Une modification étonnante de ces manifestations peut être attendue à la suite de l'application de cette méthode.

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