INTERNATIONAL JOURNAL OF LEPROSY Volume 39, Number 4
Printed in the U.S.A.

Controlled Follow-Up Assessment of the Effect of Thalidomide Upon The Ulnar Nerve in Leprosy[1, 2]

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As a result of a number of reports ([14, 15, 16, 17, 18]), thalidomide (N-phthaloylglutarimide) has been introduced in the treatment of leprosy reactions on a trial basis. According to these studies, thalidomide has an early, sometimes dramatic effect upon the pain and dermatological and neurological manifestations of the reaction. During a series of treatments carried out for periods up to four years, no serious or permanent side effects were observed ([13]). An improvement of the neuritis due to leprosy reaction, subsequent to thalidomide therapy, was found to follow the amelioration of the nerve conduction defect.

During the past decade some investigators have ascribed to thalidomide, used in conditions other than leprosy, a polyneuropathy with both sensory and motor deficit having a poor prognosis ([3, 5, 8, 9, 10]).

Because of the beneficial influence of thalidomide upon the leprosy reaction and the adverse nerve lesions reported by the above mentioned investigators, it was deemed necessary to further assess any possible effects this drug might have in leprosy, under controlled conditions, and without leprosy reaction.

1 Received for publication May 17, 1971.

2 This study was supported by Grant 19-P-58055-F-01 from the Social and Rehabilitation Services, U.S. Department of Health, Education and Welfare, Washington, D.C.

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MATERIAL AND METHOD

The follow-up examinations were initiated on 28 patients, but because of lack of cooperation on the part of some of them, only 19 are included in this report. All these patients suffered from lepromatous leprosy. This diagnosis was based on the skin manifestations, positive bacteriologic smears, histologic evidence and a negative lepromin test.

These trials were performed on patients suffering from the lepromatous type only, 1) in order to avoid possible variations due to the different kinds of nerve lesions encountered in other forms of leprosy, 2) because this form is prevalent in Israel, and 3) because nerve lesions are common and either the nerve trunk or its branches may be selectively damaged. These 19 patients were divided into two groups, one treated with sulfones and thalidomide, and the second, the control group, by sulfones only. The thalidomide group consisted of 13 patients; 12 men and one woman, aged 17-68 years. They had had leprosy for known periods of four to twenty-nine years. Their treatment consisted of sulfones (DDS) 25-50 mg/day and thalidomide 400 mg/day. Of these, seven showed various degrees of disease activity throughout the period of investigation and six were inactive.

The control group consisted of six patients; four men and two women, aged 25-49 years, who had had leprosy for periods from six to twenty-four years. Their treatment consisted of sulfones only (DDS) 25-50 mg/day. Of these, one was active and five were inactive. The uneven number of patients in the two groups was caused by the elimination, previously mentioned, of uncooperative subjects. During this investigation, none of the 19 patients had manifestations of leprosy reaction.

The follow-up period was for one year. Each patient underwent a dermatologic, neurologic and electric nerve stimulation examination before the trial, and at six month intervals. The dermatologic examination included bacteriologic smears and lepromin tests.

In previous studies ([11,13]) it was found that in most patients, in whom clinical or electricity elicited lesions of the peripheral nerves are apparent, the ulnar is in general the earliest and most damaged nerve. For this reason it was decided to limit the neurologic and electric examination to this nerve only. The muscle power of each individual muscle innervated by the ulnar nerve and the integrity of its sensory territory were examined on both sides. It was necessary to examine both sides because in previous ([11, 13]) and in the present investigation, marked differences were found between the two ulnar nerves in regard to the condition and behavior of lesion. For this reason, too, the results are related to the total number of nerves examined, and not to the patients themselves.

The electrical tests consisted of motor (MNC) and sensory (SNC) nerve conduction. These two tests have already proven to be reliable and sensitive indicators of the condition of the nerve in many conditions ([2, 4, 6, 7]) and in leprosy ([13]). Furthermore, they are easily performed and do not cause undue discomfort to the patient. Briefly, the technic for MNC was as follows: a coaxial teflon-coated needle electrode was inserted in the abductor digiti minimi for the pick-up of the response. The evoked response was visually displayed on an oscilloscope provided with electronic memory (for photography) and tape recorded for further reference. The supramaximal impulses, from a constant voltage stimulator (up to 200 V.) had a frequency of 1/sec (1 pulse per second) and duration of one millisecond. Each examination included stimulation from the proximal point of the ulnar nerve (above the medial condyle of the humerus) and the distal point (slightly medial on the palmar aspect of the wrist). The evoked responses were superimposed on the oscilloscope in order to ascertain their regularity.

The technic for SNC according to Bauwens ([1]), as modified by us, was as follows: the two recording electrodes, consisting of loops of copper, were placed on the metacarpophalangeal and proximal interphalangeal joints of the fifth finger. Ground contact was provided by a silver stretch strap placed around the palm of the hand. The stimuli, from a constant voltage stimulator, were submaximal, with a frequency of 1/sec and two durations, of 1.0 msec and 0.3-0.5 msec for the proximal and distal point respectively. The relatively low durations were necessary for a lower stimulus artefact. The proximal and distal points were almost the same as for the SNC. Each test was carried out at least twice at each examination. All the neurological and electrical examinations were carried out in the laboratory, which was kept at a constant, comfortable temperature.

As analysis of the results and comparison of the trend of the nerve lesion required grouping of the electrical tests, it was decided to arbitrarily classify the values of nerve conduction (NC) into five basic grades. This, however, raised another problem related to MNC, namely that in some cases the velocity could not be used because the selective damage of either the nerve trunk or of its distal branches only tended to falsify the calculations of velocity. For this reason, only the delays of MNC from the proximal (at the elbow level) and distal points (at the wrist level) were analyzed. A second difficulty was that of defining a "normal" delay, in consideration of the variable individual distances between electrodes. This was finally defined as the average value of delay found in healthy individuals from the maximal distance found in our patients (39 cm and 11 cm respectively). These problems did not exist in SNC in which the velocity could be used. Accordingly, arbitrary gradings were defined as normal, borderline, abnormal-mild, abnormal-moderate and abnormal-severe. Their exact definitions appear in Table 1.

In order to avoid possible bias, the results of the electrical tests were known only to the team which carried them out, while the type of therapy (thalidomide or not) was

TABLE 1. *Definitions for the arbitrary gradings of MNC and SNC—ulnar nerve.*

Grading	MNC delay (in msec.) Proximal	Distal	SNC Velocity (in m/s)
Normal	up to 8.0	up to 4.0	61 and higher
Borderline	8.1– 9.0	4.1–4.5	51–60
Abnormal-mild	9.1–11.0	4.6–5.0	41–50
Abnormal-moderate	11.1–13.0	5.1–6.0	31–40
Abnormal-severe	over 13.1	over 6.1	under 30

known by the dermatologic team only. The results were compared according to thalidomide-treated or control groups at the end of the one year of investigation only. The only selection of patients was on the basis of suffering from lepromatous leprosy and obtaining an evoked electrical response. A pathologic value of MNC or SNC before the investigation, on one or both sides, was not considered a contraindication as it still allowed comparison of the trend of lesion.

RESULTS

During the one year of investigation, no dermatologic or laboratory changes occurred in the condition of the patients as compared with the initial examination, and none of them had a leprosy reaction.

There were, however, a number of vacillations in the neurologic status, both motor and sensory. These were found to closely follow the changes in MNC and SNC. For this reason, the following results will relate to the electrical tests only, as the clinical neurological signs would not provide additional information.

As the changes noted in the electrical tests were gradual, some results will compare the initial and last examinations only. Because the number of patients and tests involved is too small, no percentages or statistical evaluation will be introduced.

The delay of MNC from the proximal point (Table 2) shows that no obvious changes occurred in the control group, while in the thalidomide group there was a tendency towards improved values. Of the initial eight abnormal-severe, only four remained so on last examination. In the abnormal-mild group there were initially six while in the last there were twelve.

TABLE 2. *Delay of MNC from the proximal point in thalidomide-treated and control patients.*

	EXAMINATION			
	Initial		Last	
Delay-Proximal point	Thalidomide[a]	Control[b]	Thalidomide	Control
Normal	—	3	1	3
Borderline	4	1	1	1
Abnormal-mild	6	3	12	3
Abnormal-moderate	4	—	4	—
Abnormal-severe	8	3	4	3
Total	22	10	22	10

[a] In 12 patients
[b] In five patients

TABLE 3. *Delay of MNC from the distal point in thalidomide-treated and control patients.*

Delay-Distal point	EXAMINATION			
	Initial		Last	
	Thalidomide[a]	Control[b]	Thalidomide	Control
Normal	8	5	13	7
Borderline	5	—	1	—
Abnormal-mild	1	1	1	—
Abnormal-moderate	2	—	1	—
Abnormal-severe	6	5	6	4
Total	22	11	22	11

[a] In 12 patients
[b] In six patients

A similar though less pronounced tendency may be noted in both groups of patients in the delay of MNC from the distal point (Table 3).

As, however, these two tables present results without possible information about the fate of individual nerves, a comparison of the trend of delay, on repeated examinations, was carried out (Table 4). "Better" and "worse" imply a shift of at least one grading, while "no change" signifies that the value found remained in the same grading. As may be seen, the majority of nerves in thalidomide-treated patients remained without change, or improved, while the great majority of controls remained without change.

It has been stressed that discrepancies were found in the trend of the lesion between the delay of MNC from the proximal and distal points. This finding is obvious from Table 5, in which all the variations encountered are presented. A similar trend from both points of examination (for 'better' or for 'worse') was found in 11 of the 22 in the thalidomide group and 6 of 10 in the controls. The discrepancy was not as marked as it appears to be from this table because one value in the distal—no change, and one in the proximal—no change were normal. Even so, it is striking that such a high number of tests should show a different trend of lesion at the two points of examination of the same nerve. The next important consideration was to observe the fate of those nerves in which the initial MNC was normal (Table 6) or abnormal-severe (Table 7). Of the eight

TABLE 4. *Comparison of delay of MNC on repeated examinations from the proximal and distal points in thalidomide-treated and control patients.*

Comparison	Point of Examination			
	Thalidomide[a]		Control[b]	
	Proximal	Distal	Proximal	Distal
Better	8	8	2	2
No change	8	9	6	8
Worse	6	5	2	1
Total	22	22	10	11

[a] In 12 patients
[b] Proximal in five patients, distal in six

TABLE 5. *Relation between trend of MNC from proximal and distal points and thalidomide-treated and control patients.*

Trend	Thalidomide	Control
Same trend in both points	11	6
Proximal better-distal no change	2	2
Proximal better-distal worse	1	—
Proximal worse-distal no change	3	—
Distal better-proximal no change	2	1
Distal better-proximal worse	1	1
Distal worse-proximal no change	2	—
Total	22	10

normal values of delay from the distal point in the thalidomide group, six remained so after one year, while two became abnormal-moderate. With one exception, there was practically no change in the control group (Table 6). Some of the initially abnormal-severe from the distal point in both the thalidomide and control groups (Table 7) showed a similar shift to better values. It is of interest that values from the distal point became normal, while the values from the proximal point shifted by one or two gradings only.

The velocity of SNC in both groups of patients appears in Table 8. In the thalidomide group it is noteworthy that of the seven nerves initially normal or borderline, only one remained so on the last examination, with a corresponding increase in the abnormal values. No such occurrence was apparent in the control group, in which a mild decrease of abnormal-severe was noted.

Comparison of SNC on repeated examinations shows that in the first period there was obvious improvement in the control group and deterioration in the thalidomide group. During the second period, however, improvement occurred in the thalidomide groups as well (Table 9).

A similar development was seen in both groups of patients with an initial abnormal-severe SNC (Table 10). The initially normal SNC were too few to allow comparison of trend.

DISCUSSION

The main purpose of this report was to observe whether thalidomide has any toxic effects upon the nerve in leprosy. Patients suffering from leprosy reaction were purposely eliminated because it has already been demonstrated that thalidomide has, in this respect, a good effect. In leprosy, however, the nerve may already be damaged and may therefore be more susceptible to further lesions caused by the drug. For this reason we have included both healthy and damaged nerves in the

TABLE 6. *Outcome of nerve condition in initially normal delay of MNC.*

	Thalidomide		Control	
	Proximal	Distal	Proximal	Distal
Last examination	Point		Point	
Normal	—	6	2	5
Borderline	—	—	—	—
Abnormal-mild	—	—	1	—
Abnormal-moderate	—	2	—	—
Abnormal-severe	—	—	—	—
Total	—	8	3	5

TABLE 7. *Outcome of nerve condition in initially abnormal-severe delay of MNC.*

Last examination	Thalidomide		Control	
	Proximal	Distal	Proximal	Distal
	Point		Point	
Normal	—	2	—	2
Borderline	—	1	—	—
Abnormal-mild	3	—	1	—
Abnormal-moderate	2	1	—	—
Abnormal-severe	3	2	2	3
Total	8	6	3	5

TABLE 8. *Velocity of SNC in thalidomide-treated and control patients.*

Velocity	First examination		Second examination[a]		Third examination[b]	
	Thalidomide	Control	Thalidomide	Control	Thalidomide	Control
Normal	4	—	1	—	—	—
Borderline	3	—	—	1	1	—
Abnormal-mild	4	1	—	1	4	2
Abnormal-moderate	5	4	4	6	12	7
Abnormal-severe	6	6	14	3	5	3
Total	22	11	19	11	22	12

[a] Six months after the initial examination.
[b] One year after the initial examination.

TABLE 9. *Comparison of velocity of SNC on repeated examinations in thalidomide-treated and control patients*

Velocity	First period[a]		Second period[b]		One period only[c]	
	Thalidomide	Control	Thalidomide	Control	Thalidomide	Control
Better	—	5	4	2	4	1
No change	5	4	6	5	8	1
Worse	6	1	1	3	3	—
Total	11	10	11	10	15	2

[a] Six months after the initial examination.
[b] One year after the initial examination.
[c] Six months after the first period or one year after the initial examination.

TABLE 10. *Outcome of nerve condition in initially abnormal-severe velocity of SNC in thalidomide-treated and control patients.*

Last examination	Thalidomide-treated	Control
Normal	—	—
Borderline	—	—
Abnormal-mild	2	1
Abnormal-moderate	5	5
Abnormal-severe	3	1
Total[a]	10	7

[a] The discrepancy in numbers (see Table 8) is explained by the fact that in four thalidomide-treated patients and one control the initial examination was at the second period.

study. The inclusion of the control group, and the performance of all the investigations on a double blind basis gives more weight to the results, in spite of the admittedly small numbers and their lack of statistical significance. In this type of study, the trend of the lesion and the comparison between values found on repeated examinations may demonstrate pathologic features with greater facility and clarity than statistical evaluations. Furthermore, the results are made more pregnant by the performance of the study under controlled conditions. By this we mean not only the double-blind technic, but also the fact that all the patients studied were suffering from one disease only, controlled by various clinical and laboratory means, in a steady condition of the disease and without suffering from other disorders which may be the cause of neuropathies (such as diabetes, peripheral vascular disease, etc.) ([4]).

Issue may be taken with regard to the length of the study (one year) as some reports mention the appearance of thalidomide neuropathy after longer periods. One year should, however, suffice for the detection of a trend in this direction, for a number of reasons: first, because all patients underwent repeated, regular examinations which could help detect signs of worsening of the nerve condition earlier than by casual, incidental examinations; second, because both MNC and SNC were examined in each patient and these tests are sensitive enough to show changes even without parallel clinical findings; third, because the inclusion of the control group, however small, could only have strengthened any finding present in the thalidomide group.

The possible objection with regard to the selection of MNC and SNC as the instruments for comparison, their arbitrary grading and their susceptibility to both intrinsic factors is valid. We have, however, tried to minimize these possible influences by standardizing the conditions. All tests were performed in the same place and under similar conditions, by the same investigators, using exactly the same technic and equipment; each test was repeated twice at each examination. Furthermore, our interest lay mainly in the direction, or trend of lesion, and not in the absolute values found.

The results obtained in this investigation seem conclusive. In this group of patients, within the one year period of study, no evidence was found that thalidomide caused any form of neuropathy. This opinion is strengthened by the following facts: similar vacillations were noted in the control group; during this period none of the patients reported any subjective complaints such as dysesthesias or paresthesias; no other peripheral nerve showed any deterioration not already obvious in the ulnar nerve.

The same gradual deterioration of the condition of the nerve, reported in previous investigations ([12, 13]) was apparent in this study as well. It was of interest to note again that, in most instances, the patient was not aware of any clinical change.

Worthy of mention is the finding, obvious in Table 5, that in leprosy there is, in some cases, a clear discrepancy in the behavior of the nerve trunk and its distal branches. It would appear that in some cases the nerve is damaged along all its fibers, in others the nerve trunk may be mildly damaged while the distal fibers are healthy, and in others the terminal nerve fibers, most probably including myo-neural junctions, are predominantly injured. The latter may be related to the type of ascending lesion,

in the form of a polymyositis, previously noted ([11]). These observations indicate the need of carrying out the examinations of nerve conduction from at least two points, as otherwise certain pathologic findings may be missed. On the other hand, the velocity of MNC should only sometimes be used in leprosy as it may be misleading. This may be related to the fact that the usual calculation of velocity is based on a type of lesion which causes an approximately uniform degree of damage and subsequent degeneration beneath the level of injury, this being a condition which does not always exist in leprosy.

SUMMARY

A possible toxic effect of thalidomide upon the peripheral nerve was sought in 13 lepromatous leprosy patients over a period of one year. The result of motor and sensory nerve conduction examinations were compared with those in six control leprosy patients, receiving sulfones only. No subjective or objective, clinical or conduction findings, indicative of a thalidomide neuropathy were detected. A gradual deterioration of the condition of the ulnar nerve was noted in some patients belonging to both groups. A discrepancy in the degree of damage and behavior of lesion between the nerve trunk and its distal branches was obvious in certain instances.

RESUMEN

Se estudió durante un perído de un año el posible efecto tóxico de la talidomida sobre el nervio periférico, en 13 pacientes con lepra lepromatosa. Se compararon los resultados de los exámenes de conduccién nerviosa sensitiva y motora con los de 6 pacientes con lepra que sirvieron de control y que recibían solamente sulfonas. No se detectaron hallazgos subjetivos ni objetivos, clínicos o de conducción, que indicaran una neuropatía debida a la talidomida.

RÉSUMÉ

Chez 13 malades atteints de lèpre lèpromateuse, on a tenté, au cours d'une période d'une année, de mettre en évidence un effet toxique éventuel de la thalidomide sur les nerfs périphériques. Les résultats des examens de la conduction dans les nerfs moteurs et dans les nerfs sensitifs ont été comparés avec ceux obtenus chez 6 autres malades de la lépre, traités par les sulfones uniquement, et pris comme témoins. Aucune des observations cliniques, objectives ou subjectives, ni aucun des examens de conduction, n'a suggéré une atteinte nerveuse due à la thalidomide. Chez quelques-uns des malades, dans l'un et l'autre groupe, on a assisté à une détérioration graduelle de la fonction du nerf cubital. Dans quelques cas, une discordance manifeste a été notée entre l'importance du dommage nerveux et l'évolution de la lésion dans le tronc nerveux d'une part, et dans ses branches distales d'autre part.

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