

Trials with Thalidomide Derivatives in Leprosy Reactions

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INTRODUCTION

The suppressive effect of thalidomide (N-thalimido-glutarimide) on lepra reactions has been proven by comparison with a placebo in direct and in double-blind studies^{1 2 3 4}. The purpose of the present study was to establish whether 1-morpholinomethyl-4-phthalimido-piperidindion-2,6 (CG603) and 1-morpholinomethyl-3-phthalimido-piperindion-2,6 (CG601), both derivatives of thalidomide, are also active.

MATERIALS AND METHODS

Five patients with lepromatous leprosy and lepra reactions were treated (Table 1).

M. leprae was present in all patients. Histological findings were in accord with the clinical picture. The Mitsuda test was negative. Of the 2 female patients, one was post-menopausal and the other a virgin. Both were continuously under gynaecological and laboratory supervision.

The patients had previously received specific treatment consisting of diaminodiphenylsulfone (DDS), diphenylthiourea (Ciba 1906), thiosemicarbazone (or TB). Previous treatment of the lepra reaction had been with antimony, steroids and thalidomide.

CG603 was given in a dose of 500 mgm. 4 times daily for 6 days. CG601 was given in a dose of 50 mgm. 4 times daily for the same length of time. These doses were in accordance with the manufacturers' recommendations. Tablets were enteric coated. Treatment was administered in separate, consecutive series, with

an interval of at least 10-20 days between each series.

RESULTS

CG603, given to 4 patients in 4 trials did not influence the lepra reaction and was considered therapeutically inactive in our 4 patients.

Thirteen trials with CG601 were carried out in 5 patients. These comprised 5 trials in one patient; 3 each in 2 patients; and one each in 2 patients. In 8 trials that lasted for a longer time, reducing the dose below 100 mgm. or, in one trial, withdrawal of the drug, was followed by a relapse. In one patient CG601 was given for 10 months, during 4½ of which the treatment was combined with sulfones. There were no new lesions in the skin.

Within the first 24 hours of treatment with CG601 there was improvement in the general condition and the patient subjectively felt better. In the next 48 hours there was resorption of the reactional skin lesions, and of the inflamed nerves. Pains diminished as did the articular symptoms. Appetite and sleep improved and the patients appeared more restful. Blood count, blood proteins, liver function tests, blood electrolytes, blood glucose, urea and transaminases remained normal during the trial periods. The blood sedimentation rates, high in all 13 trials, decreased in 4 of them from 107 to 77 mm. on one occasion, from 88 to 9, from 78 to 52 and from 50 to 30 mm. on 3 other occasions. In 9 trials there was no change in the blood sedimentation rate.

TABLE 1

Patients with Lepromatous Leprosy and Lepra Reactions treated in the present study

<i>Patient</i>	<i>Sex</i>	<i>Age</i>	<i>Duration of Leprosy (in years)</i>	<i>Duration of Lepra Reaction (in years)</i>
1	M	31	25	24
2	F	25	16	15
3	M	21	3	3
4	F	53	4	4
5	M	56	7	7

There were no changes in the lepromas. Bacteriological studies remained positive. There were no side effects even in the patient who received the drug continuously for 10 months.

Two case reports are presented in detail:—

Patient 1: E.D., a 31-year-old man with lepromatous leprosy of 25 years' duration. He had lepromas and lepra reactions and azoospermia. He had received treatment with oil of chaulmoogra, thiosemicarbazone 50-150 mgm./day, sulfones 50-100 mgm./day and diphenylthiourea 2.4 gm. daily. During the first several years of his illness he had had an almost continuous lepra reaction which had been treated with antimony and steroids. In the past 3 years he had had only 4 lepra reactions. During 3 of these he received thalidomide for from 5 to 12 days. The dose was 400 mgm. daily and the free interval from lepra reaction lasted up to 17 months. The last reaction consisted of erythema nodosum leprosum with erythema multiforme of the face, chest and extremities. There was also neuritis, arthralgia, insomnia and lack of appetite. He had a temperature of up to 39.7°C. The blood sedimentation rate was 58 mm./h. He received 2 gm. CG603 daily in addition to sulfones. No improvement ensued during the 6 days of the trial. New skin lesions appeared on the extremities and chest. His temperature rose up to 40.2°C. The blood sedimentation rate was 100 mm./h. and there was subjective deterioration. The CG603 was discontinued and CG601 was administered. Within 24 hours the temperature dropped to 37.8°C. The skin lesions and neuritis regressed and were almost completely resorbed on the sixth day of treatment. The blood sedimentation rate fell to 52 mm./h. The blood count was normal before CG601 was given and did not change.

Patient 2: N.D., a 25-year-old virgin, was hospitalised continuously for 16 years because of nodular and reactional manifestations. At various times during a period of 8 years she received 25-100 mgm. sulfones and 25.5 mgm. of meticorten per day. She was never free from lepra reactions for intervals longer than 3-4 weeks. She was given thalidomide 200-300 mgm. initially and when no improvement ensued the dose was increased to 500 mgm. At this dose there was definite improvement, and the dose

was decreased gradually to 100 mgm. daily, and for a year she was free from reactional manifestations. Relapses appeared with lower doses. After a year thalidomide was stopped and sulfones were continued. Two weeks later a lepra reaction occurred. She was given CG603 for 6 days without effect; new elements of erythema nodosum leprosum appeared and she also had neuritis, arthralgia and a fever of 39°C. The BSR was 72 mm./h., Hb 11.8 gm.%, hematocrit 35%; leukocyte count and liver function tests were normal. At this stage 150 mgm. of CG601 was given. Within 24 hours the temperature dropped to 38°C. Skin lesions began to fade, and her neuritic pains and arthralgias subsided. On the seventh day there were no lepra reaction lesions to be seen.

The BSR dropped to 30 mm./h., Hb rose to 13.3 gm.%, hematocrit to 40%. The patient received CG 601 for 10 months; for 4½ of these, treatment was combined with sulfones. The dose of CG601 was reduced to less than 100 mgm. per day on 4 occasions and each time a reaction promptly appeared. Stopping the drug was followed by an acute reaction, that responded to a daily dose of 150 mgm. CG601.

DISCUSSION

After the promising results obtained with CG601 it became important to establish whether the drug could prevent lepra reactions present in patients on sulfone treatment. It was found that 100 mgm. per day was the minimum maintenance dose in such circumstances.

In the present study the maximum dose of CG601 was 200 mgm. per day. This could account for the slowness of improvement as compared with that of thalidomide, which was given initially at a dose of 400 mgm. daily.

The pharmacodynamics of CG601 are unknown; they may resemble those of thalidomide.

SUMMARY

1. CG603 and CG601 were tried in 5 patients with lepra reactions of long standing.

2. Four patients received up to 2 gm. of CG603 daily for 6 days. There was no effect on the lepra reaction and the use of the drug was stopped.
3. Thirteen trials with a daily dose of 900 mgm. of CG601 were carried out. Five trials lasted 6 days and 8 up to 10 months. There was a beneficial effect on lepra reactions. Lowering the dose below 100 mgm. daily often resulted in a relapse.
4. There was a definite subjective and objective improvement, starting in from 24 to 72 hours. The improvement seemed to be slower than that induced by thalidomide.
5. No side effects were observed during the trial period.

CONCLUSIONS

1. In a short clinical trial on 4 patients with lepra reaction 1-morpho-linomethyl-4-phthalimido-piperidindion-2,6 (CG603) appeared to be ineffective.

2. In 13 separate trials performed on 5 patients, 1-morpholinomethyl-3-phthalimido-piperindion-2,6 (CG601) had a beneficial effect both subjectively and objectively on lepra reactions.
3. A larger scale trial of the latter drug in lepra reactions appears justified.

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