Chemotherapy of Leprosy with Newly Synthesized Thiocarbanilides*

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ABSTRACT

Attention has been paid to the thio-carbanilide derivative and the authors synthesized some new compounds of thio-carbanilides for experimental studies on tuberculosis and leprosy.

The series of newly synthesized chemical compounds of thio-carbanilides were studied for comparison with the already known antitubercular agents; INH, PAS, Streptomycin and D. D. S. The strains of Mycobacterium tuberculosis (H37Rv, Ravenel, and B. C. G.) and Mycobacterium phlei were used for the in vitro experiments. In the in vivo experiments, the strain of Mycobacterium tuberculosis var. bovis (Ravenel) was employed.

The strain of Mycobacterium leprae muriun (Hawaiian strain) was used for the murine leprosy experiments.

The experimental animals for the in vivo tests were white mice (CFW strain) and these were extensively employed in tuberculosis and leprosy as well. Sixteen cases of various types of human leprosy, were treated with one of the newly synthesized thio-carbanilides (L-4).

Among the newly synthesized chemical compounds of thio-carbanilides studied for their antituberculous and antimurine leprosy activity in vitro and in vivo experiments, two compounds were shown to be suppressive agents for those infections without significant toxicity.

These two compounds were named tentatively as L-1 and L-4.

1) LD90 of L-1 was 1.054mg/kg and that of L-4 was 1.028mg/kg, while the LD90 of INH was 650mg/kg and PAS was 4.000mg/kg orally in the experimental animals.

2) L-1 and L-4 showed remarkable suppressive activity in vitro using solid media with 100r/ml. concentration. These data were parallel to 1r/ml. of INH and 50r/ml. of PAS. The inferiority of L-1 and L-4 to INH and PAS in vitro studies might have been due to the water insolubility of these compounds while INH and PAS were readily soluble in water.

3) In vivo experiments with L-1 showed a much more superior antituberculous effect than was found with INH and PAS.

4) A method of grading the bacterial count in a homogenized tissue suspension of visceral organs (lungs, liver, spleen and kidneys) using the simple technique of the Gaffky scale was accurate and time saving technique in screening the results of the chemotherapeutic agents in tuberculosis.

5) Among the newly synthesized compounds L-4 showed the most remarkable suppressive effect on murine leprosy. The suppressive results were similar to those of INH.

6) The method of measuring the size and the weight of leproma at the inoculated site was simple and is an adequate screening test for chemotherapeutic effect in murine leprosy.

7) In the trials with human leprosy 16 cases of various types, using L-4, the effectiveness in clinical...
as well as in bacteriological improvement was remarkable.
a) After L—4 treatment decrease in bacteriological indices and remarkable clinical improvement after a relatively short period of treatment were observed.
b) L—4, up to the maximum daily dose of 500mg, can be safely administered orally to the patients without any significant side reactions.
c) L—4 could be used with remarkable clinical improvement for the patients in lepra reactions.

INTRODUCTION

In the first series of these papers (Choi and Lew, 1965), we reported the results of experimental studies on the newly synthesized thiocarbanilides for chemotherapeutic activity against Mycobacterium tuberculosis and Mycobacterium leprae murium.

The data, obtained from in-vitro and in-vivo experiment, clearly indicated that L—1 and L—4 could be used as antituberculosis and anti-leprosy drugs respectively in human cases.

This report is to present the results of L—4 medication on human leprosy patients as a clinical trial for this new drug.

METHODS AND MATERIALS

Routine examinations:

Before starting the treatment of leprosy with the newly synthesized thiocarbanilide, the following examinations were completed and results were recorded;

a) Detailed clinical and photographic records of the cases
b) Bacteriological examination of all cases, calculating the bacterial index (Ridly, 1959)
c) Lepromin test using the trypsin purified Lepromin (Lew and Carpenter, 1956) and reading the 4 weeks reaction
d) Hematological examination—total counts, differential counts of leukocytes, and estimation of hemoglobin level

e) Urinalysis

The above examinations, except the lepromin test, were repeated at regular intervals and the results were compared with the initial findings.

Methods of drug administration:

The newly synthesized drug was put into gelatin capsules and given orally to all of the patients. The drug was given daily, and the initial dose was 100mg which was gradually raised to the maximum of 500mg in maintenance dose. Oral administration of this method was found to be well tolerated except for slight gastric discomfort in a few cases.

However, such complaints were easily controlled by the administration of ordinary stomachics.

Number and selection of patients:

Patients of the lepromatous type with positive bacteriology were selected because clearer results were desired for the evaluation of the compound.

A total of 16 patients were selected for the investigation, 15 of the lepromatous and 1 of the reactional tuberculoid type. In the 15 lepromatous cases, 6 of the non-reactional, 3 of the sulfone allergic, 5 of the erythema nodosum leprosum and 1 of the neuritis only were included.

Three of lepromatous (Case No. 3, 4, and 5) and 1 reactional tuberculoid (Case No. 16) were fresh cases and given L—4 from the beginning of anti-leprosy treatment. However, the remaining 12 cases who had suffered from sulfone allergy or reactions arising from the indiscriminate use of sulfone drugs were forced to change to L—4 when the investigation was initiated.

Duration of L—4 treatment:

L—4 medication has been continued from 4 months to 14 months. The differences in the length of L—4 medication are due to the time of initiation of L—4 treatment in each case.
### Table 1. Results of the L-4 treatment to the no reactional Lepromatous cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Chart No</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Dia.</th>
<th>Bact. Index</th>
<th>Lepromin</th>
<th>Type of Lep. Reaction</th>
<th>React. Cont.</th>
<th>Medication</th>
<th>Starting Date of L-4 R</th>
<th>Duration of L-4 R</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3,269</td>
<td>44</td>
<td>M</td>
<td>L 4+ 4+</td>
<td>5+</td>
<td>No reaction</td>
<td>D. D. S.</td>
<td>Mar. 12 1965</td>
<td>8 m</td>
<td>100mg—2w 200mg—2.5m</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3,312</td>
<td>26</td>
<td>M</td>
<td>L 3+ 2+</td>
<td>5+</td>
<td>No reaction</td>
<td>D. D. S. L-4</td>
<td>Mar. 26 1965</td>
<td>11 m</td>
<td>100mg—1w 200mg—1m 300mg—7m</td>
<td>Excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3,358</td>
<td>51</td>
<td>M</td>
<td>L 4+ 4+</td>
<td>6+</td>
<td>No reaction</td>
<td>L-4</td>
<td>Mar. 26 1965</td>
<td>11 m</td>
<td>100mg—1w 200mg—1m 300mg—10m</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3,397</td>
<td>21</td>
<td>F</td>
<td>L 5+ 4+</td>
<td>6+</td>
<td>No reaction</td>
<td>L-4</td>
<td>Apr. 14 1965</td>
<td>8.5 m</td>
<td>100mg—2w 200mg—1m 400mg—5m</td>
<td>Excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3,518</td>
<td>14</td>
<td>F</td>
<td>L 6+ 6+</td>
<td>5+</td>
<td>No reaction</td>
<td>L-4</td>
<td>Aug. 6 1965</td>
<td>8 m</td>
<td>25mg—1w 50mg—2w 100mg—3w 200mg—4w 150mg—2.5m</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3,262</td>
<td>43</td>
<td>M</td>
<td>L 4+ 3+</td>
<td>5+</td>
<td>No reaction</td>
<td>D. D. S. L-4</td>
<td>Feb. 19 1965</td>
<td>8 m</td>
<td>100mg—1m 150mg—2w 300mg—3.5m 300mg—3m</td>
<td>Better</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Results of the L-4 treatment to the Erythema Nodosum Leprosum cases

<table>
<thead>
<tr>
<th>Case No</th>
<th>Chart No</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Dia.</th>
<th>Bact. Index</th>
<th>Lepromin</th>
<th>Type of Lep. Reaction</th>
<th>React. Cont.</th>
<th>Medication</th>
<th>Starting date of L-4 R</th>
<th>Duration of L-4 R</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>516</td>
<td>49</td>
<td>F</td>
<td>L 5+ 3+</td>
<td>5+</td>
<td>E.N.L. 4y</td>
<td>D. D. S. Prednisolone</td>
<td>Feb. 19 1965</td>
<td>10.5 m</td>
<td>100mg—2w 200mg—2m 300mg—4m 400mg—2m</td>
<td>Excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>418</td>
<td>11</td>
<td>M</td>
<td>L 5+ 3+</td>
<td>5+</td>
<td>E.N.L. 5m</td>
<td>D. D. S. B.T. 8 L-4</td>
<td>Apr. 12 1965</td>
<td>11 m</td>
<td>100mg—1w 200mg—2m 300mg—3m 400mg—3m</td>
<td>Better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2,428</td>
<td>11</td>
<td>F</td>
<td>L 5+ 3+</td>
<td>5+</td>
<td>E.N.L. Neuritis 3y</td>
<td>D. D. S. I.N.H. 1963 Operation</td>
<td>Jun. 8 1964</td>
<td>1y</td>
<td>100mg—2m 300mg—4m 800mg—2.5m</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1,691</td>
<td>29</td>
<td>M</td>
<td>L 5+ 3+</td>
<td>5+</td>
<td>E.N.L. Neuritis 5m</td>
<td>D. D. S. I.N.H. Operation</td>
<td>Dec. 4 1964</td>
<td>1y</td>
<td>100mg—2w 200mg—3m 300mg—6m 400mg—2m</td>
<td>Excellent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>910</td>
<td>27</td>
<td>F</td>
<td>L 2+ 1+</td>
<td>5+</td>
<td>E.N.L. Progressive Lepra reaction 1y</td>
<td>D. D. S. Prednisolone</td>
<td>Mar. 5 1965</td>
<td>7 m</td>
<td>100mg—1w 200mg—2m 300mg—3.5m 400mg—2.5m</td>
<td>Excellent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *) B. T.: Blood transfusion
Table 3. Results of the L-4 treatment to the lepra reaction cases other than E.N.L.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Chart No.</th>
<th>Age</th>
<th>Sex</th>
<th>Type of Dis.</th>
<th>Bact. Index</th>
<th>Lepromin</th>
<th>Type of Leprosy</th>
<th>React. Cont.</th>
<th>Medication</th>
<th>Starting date of L-4 R</th>
<th>Duration of L-4 R</th>
<th>Dosage of L-4/day</th>
<th>Evaluation of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>3,245</td>
<td>33</td>
<td>M</td>
<td>L</td>
<td>5+</td>
<td>1</td>
<td>Sulfone allergy</td>
<td>1m</td>
<td>D, D, S, L-4</td>
<td>Jun. 22, 1965</td>
<td>1 Y 2m</td>
<td>150mg-1w, 300mg-1m</td>
<td>Stationary</td>
</tr>
<tr>
<td>13</td>
<td>3,522</td>
<td>28</td>
<td>F</td>
<td>L</td>
<td>5+</td>
<td>1</td>
<td>Sulfone allergy</td>
<td>2w</td>
<td>D, D, S, (2w) L-4</td>
<td>Aug. 27, 1965</td>
<td>4,5m</td>
<td>50mg-1w, 100mg-1w, 150mg-2w, 200mg-2m, 300mg-1m</td>
<td>Excellent (Suicide)</td>
</tr>
<tr>
<td>14</td>
<td>3,589</td>
<td>26</td>
<td>M</td>
<td>L</td>
<td>3+</td>
<td>1</td>
<td>Sulfone allergy</td>
<td>2m</td>
<td>D, D, S, (1m)</td>
<td>Dec. 17, 1965</td>
<td>4m</td>
<td>100mg-2m, 150mg-2m</td>
<td>Good</td>
</tr>
<tr>
<td>15</td>
<td>2,562</td>
<td>31</td>
<td>M</td>
<td>L</td>
<td>4+</td>
<td>2</td>
<td>Neuritis</td>
<td>9m</td>
<td>D, D, S, B, T,</td>
<td>Nov. 19, 1965</td>
<td>4m</td>
<td>100mg-2m, 200mg-2m</td>
<td>Better</td>
</tr>
<tr>
<td>16</td>
<td>3,520</td>
<td>20</td>
<td>M</td>
<td>T</td>
<td>-</td>
<td>+</td>
<td>React. tuber.</td>
<td>2m</td>
<td>L-4</td>
<td>Aug. 13, 1965</td>
<td>7m</td>
<td>100mg-2w, 200mg-2m, 250mg-1.5m, 300mg-3m</td>
<td>Good</td>
</tr>
</tbody>
</table>

(*) B.T.: Blood transfusion

**Evaluation of L-4 treatment:**

Table 4 summarises the criteria used for the evaluation of L-4 treatment.

Table 4. Criteria of the evaluation

<table>
<thead>
<tr>
<th>Indentity</th>
<th>Decrease in bacteriologic index</th>
<th>Clinical improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stationary</td>
<td>± or 0</td>
<td>±</td>
</tr>
<tr>
<td>Good</td>
<td>+ or ±</td>
<td>± or +</td>
</tr>
<tr>
<td>Better</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Excellent</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**RESULTS**

For convenience in evaluating the results of the clinical trial with L-4 the patients were divided into 3 groups as follows;

- **Group I:** Six of lepromatous cases who did not have any reaction. (Table 1)
- **Group II:** Five of lepromatous type who were in a state of E.N.L alone or with some other complication. (Table 2)
- **Group III:** Four of lepromatous and 1 of tuberculoid type who were in a state of sulfone allergy, neuritis, or reactional tuberculoid when L-4 treatment was begun. (Table 3)

Throughout the course of L-4 treatment all of the patients have been checked with routine examinations at regular intervals (see Methods and Materials). So far, no significantly abnormal findings in the examinations have been observed. This fact implies that L-4 medication up to the maximum dose of 500mg per day can be safely administered without any significant side reaction. The maximum dose of 500mg per day was arbitrarily derived from the LD50 dose in mice 1,000 mg per kg.

The evaluation of the clinical status of the L-4 treated cases was made according to the criteria of evaluation (Table 4). The criteria included the decrease in the bacteriological index and clinical improvement.

**Bacteriological Improvements:**

Decreases in the bacteriological index were observed in 10 out of 15 patients after a relatively
short period of L—4 treatment ranging from 4 months to 1 year.

This effect was most pronounced in Group II (E. N. L.) and Group III (sulfone allergy and others). In these groups, two grade decreases in bacteriological indices were the most common feature. These remarkable decreases in bacteriological indices were attained after 4 months to 1 year of L—4 treatment.

The decrease in the bacteriological index was not so marked in Group I as in Group II and III. Only one grade decrease was observed in the bacteriological index in 3 out of 6 patients in this group, and the bacteriological indices in the remaining half of 6 patients were without any decrease after 8 to 11 months of L—4 medication.

Clinical Improvements:

In general, clinical improvement was much more evident than the decrease in bacteriological index when L—4 was used. Clinical improvements included better general condition, subsidence or decrease in the extent or degree of macules and nodules, alleviation of neuritic symptoms and so on. By the criteria shown in table 4, only one case out of the 16 patients so far treated could be graded as “Stationary”, 6 cases as “Good”, 3 cases as “Better” and 6 cases as “Excellent” in the evaluation of L—4 treatment (See table 1, 2, and 3).

DISCUSSION

Various kinds of thiocarbanilide derivatives have been synthesized and the effectiveness of the drugs as antileprosy chemotherapeutics have been evaluated in clinical trials by many investigators (Buu-Hoi, 1954; Loginov et al., 1963; Davey, 1958; Davey and Currie, 1956). Among these, Dialide, Etoxid and Su—1906 are now in use.

To our knowledge, L—4 newly synthesized by authors, is the latest derivative of thiocarbanilides so far developed. The clinical trial of L—4 in human leprosy seemed very encouraging because of its significant antileprosy effects in-vivo and in-vitro experiments as shown in the first series of these papers (Choi and Lew, 1965).

Both bacteriological and clinical improvement observed in this limited clinical trial were quite remarkable. The new drug was well tolerated by all of the patients except minor gastric discomfort in a few cases. It also appears that lepra reactions which are frequently associated with leprosy treatment could be effectively managed by the administration of L—4.

However, it may be dangerous to make certain conclusions on the therapeutic value of L—4 medication in leprosy patients from the results obtained from 16 selected leprosy patients.

Comparative studies of L—4 with D. D. S., Su—1906 and other antileprosy drugs were beyond the scope of this limited investigation. From the data available, it might be concluded that L—4 is significantly effective in the treatment of lepromatous leprosy in comparison with the results from D. D. S., Su—1906 or other antileprosy drugs at present.

Finally, it should be added that this is a rather preliminary report of the clinical trial of L—4 in leprosy treatment, and that definite and conclusive evaluation of L—4 treatment in human leprosy will have to wait until a more extensive investigation can be carried out in the future.

CONCLUSION

Total of 16 leprosy patients, 15 of lepromatous type and 1 of tuberculoid type, were treated with a newly synthesized thiocarbanilide, L—4.

Evaluation of the L—4 treatment was made on the basis of a decrease in the bacteriological index and clinical improvement. The results of this study were summarized as follows:

1. After L—4 treatment decrease in bacteriological indices and remarkable clinical improvements
after relatively short period of treatment was observed.

2. L-4, up to the maximum daily dose of 500 mg, can be safely administered orally to the patients without any significant side reactions.

3. L-4 could be used with remarkable clinical improvement for the patients in lepra reactions. From the results of the above small scale clinical trial, this compound appears to be worthy of investigation in larger and planned projects.

REFERENCES


