COMPARISON OF DIAMINODIPHENYLSULFONE AND THIOSEMICARBAZONE IN THE TREATMENT OF LEPROMATOUS LEPROSY

CLINICAL AND BACTERIOLOGICAL EVALUATION IN SIXTY HOSPITALIZED PATIENTS

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The recent introduction of diaminodiphenylsulfone (DDS) and the thiosemicarbazones represents a significant contribution in the treatment of leprosy. The efficacy of DDS has been confirmed by a number of well-controlled observations (1, 2, 4, 5, 8, 10, 11). The effectiveness of thiosemicarbazone still remains to be evaluated (3, 7, 9, 12, 13, 14). For both drugs, the periods of observation have been brief.

In the present report a comparison is made of the clinical and bacteriological results obtained in 60 cases of lepromatous leprosy treated as inpatients at the Hospital for Hansen's Disease in Jerusalem, with DDS or thiosemicarbazone or with DDS followed by thiosemicarbazone. The observations indicate that both drugs influence leprosy favorably, and that thiosemicarbazone is somewhat more efficacious than DDS.

MATERIALS AND METHODS

Diaminodiphenylsulfone \(^1\) was given orally to 27 patients. Each patient received 100 mgm. daily during the first week, 200 mgm. daily the second week, and 300 mgm. the third week and thereafter. No drug was given during the fourth week, or during the last week of each subsequent month. This group of patients was treated for 24 months.

Two kinds of thiosemicarbazones were used, the para-acetylaminobenzaldehyde \(^2\) and the para-ethylsulphenylbenzaldehyde \(^3\) forms, these being given orally to 21 patients. The initial dose was 25 mgm. daily, the dosage being increased gradually to 150 mgm. and maintained at this level.

\(^1\) Avlosulfon, Imperial Chemical Pharmaceuticals Ltd.
\(^2\) Thiacetazone or Neustab, Boots Pure Drug Co.; Thioparamizone, Herts Pharmaceuticals Ltd.; and Phthisoral, Daphearme.
\(^3\) Ethizone, Herts Pharmaceuticals Ltd.
During the last week of each month no drug was given. The treatment periods of these patients varied from 6 to 16 months.

One group of 12 patients treated with DDS for 2 years had improved to some extent clinically, but then had become stationary during the last few months of that treatment. They were then transferred to thiosemicarbazone therapy, which had continued for 6 to 16 months at the time of this report.

The clinical results were classified as follows: (a) cleared, all skin lesions disappeared; (b) markedly improved, approximately 90 per cent of the skin lesions disappeared; (c) slightly improved, about 50 per cent of the skin lesions disappeared or diminished in size; (d) stationary; (e) worse, there being an increase in number or in size of lesions, or both.

The bacteriological results were graded as follows: (a) 4+, masses of bacilli and many globi per field; (b) 3+, some globi and more than 10 bacilli per field; (c) 2+, not more than an average of 10 bacilli per field; and (d) 1+, solitary bacilli found only after prolonged search.

From June 1951 until June 1952 bacteriological examinations were made systematically on all of the patients. Every three months slides were made from the earlobe and the nasal mucous membrane. A total of 77 biopsies were made at irregular intervals, and smears were made from the operation wounds. The regular Ziehl-Neelsen stain, and that procedure as modified by Freire and Ramos (6) and by Wilkinson (15) were employed. Blood, urine and liver-function examinations were performed at regular intervals before and during therapy.

Regarding the status of the cases at the beginning of treatment, each group contained some previously untreated patients with active lesions, and others who had been treated and whose lesions appeared inactive. From the tabulated data it will be seen that all of the latter group remained unchanged. Furthermore, in the DDS and thiosemicarbazone groups some patients of the active subgroups were bacteriologically negative at the outset. These were lepromin-negative patients with macular lesions which were found histologically to be lepromatous or prelepromatous. Some leprologists would doubtless call such cases "indeterminate," but on the basis of the negativity to lepromin and the lepromatous histology we classify them as lepromatous even when bacilli are so few that they are not demonstrable in smears.

RESULTS

The clinical and bacteriological results are summarized in Tables 1 and 2, each of which is divided into three sections for the different treatment groups.

Of the 27 patients which received DDS, 14 had not been treated previously for leprosy, and their lesions were active. Eleven of these 14 were clinically cleared or markedly im-
TABLE 1.—Clinical results obtained in cases of lepromatous leprosy with the different treatments employed.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>No. of cases</th>
<th>Improved</th>
<th></th>
<th>Stationary</th>
<th>Worse</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cleared</td>
<td>Markedly</td>
<td>Slightly</td>
<td></td>
</tr>
<tr>
<td>Diaminodiphenyl sulphone, 2 years, 27 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>14</td>
<td>4</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Inactive</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Thiosemicarbazone, 6-16 months, 21 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>17</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Inactive</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Diaminodiphenyl sulphone followed by thiosemicarbazone, 12 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>11</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Inactive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 2.—Bacteriological findings before and after treatment with the different drugs employed.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>No. of cases</th>
<th>Before treatment</th>
<th>After treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>No change</td>
</tr>
<tr>
<td>Diaminodiphenyl sulphone, 2 years, 27 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>14</td>
<td>19</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Inactive</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Thiosemicarbazone, 6-16 months, 21 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>17</td>
<td>16</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Inactive</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diaminodiphenyl sulphone followed by thiosemicarbazone, 12 cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>11</td>
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<td>0</td>
<td>7</td>
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<tr>
<td>Inactive</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
proved. Five of them were also improved bacteriologically, and
four remained negative. Thirteen patients had received treat­
ment previously, either compound sulfones or chaulmoogra oil,
and had no active skin lesions. Five of these were improved
bacteriologically and eight remained negative.

Of the 21 patients who received thiosemicarbazones, 17 had
never been treated previously and had active lesions. Nine of
these were cleared or markedly improved, and 6 were slightly
improved. Nine showed bacteriological improvement, and 1 re­
mained negative. In this group only 4 patients had been treated
previously by other drugs and had no active skin lesions. Bac­
teriologically, 3 of them became negative and 1 remained neg­
ative.

Eleven of the group of 12 patients who received DDS fol­
lowed by thiosemicarbazone had active skin lesions at the time
of the change of treatment. Of these 11, 10 showed further
clinical improvement, and 4 were improved bacteriologically.
The 1 patient without active lesions remained unchanged in
status.

Toxicity.—Toxic effects occurred with the use of both drugs,
but they were of minor importance. Five patients, who were
excluded from the total of 60, did not tolerate either the com­
pound sulfones, or DDS, or thiosemicarbazone, suffering from
violent lepra reactions after taking any of these drugs. One
of them developed an urticarial rash and swelling of the face,
extremities and trunk. Of the 60 patients recorded here, several
complained of transient headache and epigastric distress. More
than one-half developed erythema nodosum-like lesions during
treatment with either DDS or thiosemicarbazone, but the treat­
ment was continued in all but 2. Occasionally the dosage had
to be reduced, or the treatment interrupted for several days,
because of these toxic reactions.

Laboratory tests.—In all 60 patients there was a variable
decrease in the number of erythrocytes and in the hemoglobin
values during the treatment. The average decrease of red cells
was approximately 1,000,000, with a corresponding decrease of
hemoglobin. The anemia due to treatment could easily be in­
fluenced by simultaneous administration of iron, liver and vita­
mins. Under these circumstances it was not necessary to stop
treatment. The white blood cells showed no changes, and no
patient developed agranulocytosis.

Routine examinations revealed albumin in the urine of 2
patients. Liver function tests (Takata-Ara, thymol turbidity,
cephalin flocculation) were performed before commencement of treatment. In almost all patients one or more of the tests were positive, and consequently they were of little help in evaluating functional hepatic damage.

**DISCUSSION AND CONCLUSIONS**

The observations of the present study suggest that thiosemicarbazone is as effective as DDS in the treatment of leprosy, and probably even more effective, although the numbers of observations are too few to be evaluated statistically. The tables show that the improvement, clinical and bacteriological, was similar with the use of either drug. However, the thiosemicarbazones were employed for only 6 to 16 months, while the DDS group was treated for 24 months. The results therefore suggest that thiosemicarbazone is more effective than DDS, since equally good improvement was obtained in a shorter period of time.

Subsequent use of thiosemicarbazone in patients who had ceased to improve under the treatment with DDS was found to be beneficial clinically in ten of eleven patients, and bacteriologically in 5 of 12.

Both drugs caused toxic effects of the same type and to the same extent. Most side reactions were of minor importance and transitory, or could be corrected under hospital conditions.

In general, the good results obtained by the use of DDS, thiosemicarbazone or both have corroborated findings reported by others. These agents are valuable additions to the therapeutic armamentarium. They arrest the disease and improve the clinical and bacteriological status of the leprous patient.

**SUMMARY**

The results of treatment of 60 hospitalized lepromatous cases with diaminodiphenylsulfone, thiosemicarbazone, or both, are evaluated clinically and bacteriologically. Twenty-seven patients were treated with DDS for a period of two years, and 21 patients with various thiosemicarbazones for periods of from 6 to 16 months. Twelve patients received DDS followed by thiosemicarbazone. Marked clinical and bacteriological improvement was observed in the majority of the patients. Toxic effects were common, but of minor importance in most instances. Five patients not included in this report did not tolerate compound sulfones, DDS or thiosemicarbazone.

The thiosemicarbazones proved to be as effective as, or even superior to, diaminodiphenylsulfone.
ACKNOWLEDGMENT

For the generous provision of drugs used in this study we wish to acknowledge the kind cooperation of Dr. W. A. R. Thomson, of the Boots Pure Drug Company; Rapharm, Ramat Gan; Dr. D. McAnally, of the Herts Pharmaceuticals Ltd.; and Imperial Chemical (Pharmaceuticals) Industries.

RESUMEN

Se evaluaron los resultados del tratamiento con dianimodiphenyl-sulfone, thiosemicarbazone o ambas drogas, en 60 pacientes lepromatosos hospitalizados, usando métodos clínicos y bacteriológicos. Fueron tratados con DDS por 2 años 27 pacientes, y con varios thiosemicarbazones 21 pacientes por períodos de 6 a 16 meses. Doce pacientes recibieron DDS seguido por thiosemicarbazone. Se observó gran mejora en la mayoría de los casos. Efectos tóxicos, aunque comunes, fueron de poca importancia en la mayoría. Cinco pacientes, no incluidos en este reporte no toleraron las sulfonas, el DDS, ni thiosemicarbazone. Los thiosemicarbazones fueron tan eficaces, o aún superiores a DDS.

REFERENCES