ONCHOCERCIASIS: A STUDY ON THE RELATION BETWEEN LABORATORY DATA AND REACTIONS ELICITED BY DIETHYLCARBAMAZINE

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Received May 2 1984/Accepted September 28 1984

Abstract: Parasitological, haematological, immunological and clinical examinations were carried out on 29 Guatemalan patients with onchocerciasis. The patients were given diethylcarbamazine (DEC) treatment (5 mg/kg/day for 7 days) and then examined clinically the adverse reactions at 3, 12, 24, 48 and 72 hours after the initial administration of DEC. The essential features of the adverse reactions elicited by DEC administration were pruritus, rash, pain, lymphadenopathy and edema. The severity of those reactions was found to be roughly proportional to the eosinophil counts in blood and/or the serum level of Onchocerca volvulus-antigen specific IgG.

Introduction

Since Mazzotti reported that diethylcarbamazine (DEC) produced rather severe adverse reactions in the patients with onchocerciasis (Mazzotti, 1948), difficulties have been experienced in the use of DEC in mass treatment. The reactions were especially dangerous if the patients were heavily infected or debilitated (Buck, 1974; Fuglsang and Anderson, 1974; Bryceson et al., 1977). Hawking (1952) reported that these reactions were presumably due to the destruction of microfilariae with the liberation of antigens which excited allergic response in patients. Garner et al. (1973) reported that the damaged microfilariae of O. volvulus or their products were not toxic when injected into normal animals, and therefore it was unlikely that these reactions were caused by themselves alone. There have been some haematological and immunological studies on the pathogenesis and the mechanisms of inflammatory reactions in the patients with onchocerciasis following DEC administration (Rodger, 1962; Henson et al., 1979; Guerra-Caceres et al., 1980). However, little is known on the relation between laboratory data before drug administration and the adverse reactions elicited. The present study aimed at the clarification of this point.

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MATERIALS AND METHODS

Twenty-nine male patients were from the plantation “San Pedro Corona” in Chicacao Suchitepequz located southwest of the endemic area of onchocerciasis in Guatemala. Their age varied from 16 to 70 years old (average; 36.1 years old). Two skin snips were taken from the left scapular and iliac regions by a Holth type corneoscleral punch. Microfilarial density (MFD) was expressed as a total number of microfilariae (mf) emerged from two 10 mm² skin snips. Of these patients 24 were positive for microfilariae of O. volvulus by skin snip (mean MFD, 77.2/two 10 mm²), and 22 were positive for onchocercoma by palpation. The patients were classified into following four groups according to MFD; negative, low (1 to 50 mf), moderate (51 to 100 mf) and high density (101 and more) groups. They were treated with a single dose of pyrantel pamoate (Combantrin) at the dosage of 10 mg/kg body weight in order to expel intestinal parasites three weeks before the administration of DEC. All patients were admitted to National Amatitlan Hospital in Guatemala during treatment and examination period. Just before DEC administration, a total number of white blood cells (WBC) per cubic millimeter of blood from cubital vein was counted by conventional method and differential cell count was assessed in the smear after Giemsa staining. The O. volvulus specific IgG was assayed by enzyme-linked immunosorbent assay (ELISA) using adult O. volvulus antigen before the initial dose of DEC. The amount of serum IgG was represented by optical density (OD).

The procedure was described elsewhere (Korenaga et al., 1983). The patients were then given the oral dose of DEC (Hetrazan) at 5 mg/kg/day for 7 consecutive days. The adverse reactions were checked at 3, 12, 24, 48 and 72 hours after the initial administration of DEC. The reactions were classified into following four groups according to the severity.

- No reaction (0): No recognizable signs and symptoms.
- Mild reaction (+): Pruritus alone.
- Moderate reaction (++): More than two clinical manifestations among pruritus, rash, pain and lymphadenopathy.
- Severe reaction (+++): Edema and at least one of the following clinical manifestations; pruritus, rash, pain and lymphadenopathy.

The association between systemic complications and laboratory data was studied by using measures of association for I × J Tables in “Discrete Multivariate Analysis: Theory and Practice” edited by Bishop et al. (1975).

RESULTS

Table 1 summarized the chronological changes in the clinical manifestations during DEC treatment. The essential feature of the clinical manifestations during DEC treatment were shown as follows; pruritus, rash, pain, lymphadenopathy and edema. Twenty-six of 29 patients experienced one or more of these manifestations.
Of 29 patients 25 experienced pruritus during this observation period, among them 16 complained the itching within three hours after the first dose of DEC (55%). At 24 hours, this rate reached the maximum (86%). After 48 hours, the number of patients with pruritus gradually decreased. Only in a few patients rash, pain, lymphadenopathy and edema were noted at three hours, while at 24 hours, the frequency of these manifestations reached 59, 34, 34 and 38 per cent respectively. Even after 48 hours, the frequency remained rather high. The pruritus appeared at various regions such as the face, neck, upper body and upper limbs. The rash was localized in the chest, scapular regions and upper limbs in most patients. The lymphadenopathy was noted more frequently in the inguinal region than the axillar one. The edema was localized in the face, chest and upper limbs, and when it appeared on the face, it was markedly severe than that in the other parts.

The relation between MFD and the severity of those adverse reactions is shown in Table 2 (V=0.391,  0.154). Out of 11 patients with high MFD, six experienced the severe (||), four experienced the moderate (±) and one patient showed mild (+) reaction. Of 13 patients with moderate and low MFD (1-100), five showed severe reaction.

Table 2  Relation between the microfilarial density and adverse reactions seen in DEC treatment (29 patients)

<table>
<thead>
<tr>
<th>MFD*</th>
<th>No. of case</th>
<th>Grade of reaction</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>1-50</td>
<td>10</td>
<td>2</td>
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<tr>
<td>51-100</td>
<td>3</td>
<td></td>
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<tr>
<td>100&lt;</td>
<td>11</td>
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</tr>
</tbody>
</table>

* Number of microfilariae in two 10 mm² snips.

Among five cases of the microfilaria negative group, four patients showed no or mild reactions. The total number of WBC of the patients ranged from 7,000 to 18,000/mm³ (mean; 9,790±2,290/mm³) before DEC treatment. Of 11 patients
whose WBC counts were 10,000/mm³ or more, 4 (36.4%) showed severe reaction (‡‡). On the other hand, out of 18 patients with WBC counts less than 10,000/mm³, 7 (38.9%) showed severe reaction (Table 3; \( V = 0.374, \hat{\sigma} = 0.131 \)). Eosinophil counts in the all patients were higher than the normal level, ranging from 660 to

<table>
<thead>
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<th>WBC counts/mm³</th>
<th>No. of case</th>
<th>Grade of reaction</th>
</tr>
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<tbody>
<tr>
<td>&lt;8,000</td>
<td>7</td>
<td>3 3 1</td>
</tr>
<tr>
<td>8,000–10,000</td>
<td>11</td>
<td>2 3 6</td>
</tr>
<tr>
<td>10,000&lt;</td>
<td>11</td>
<td>1 2 4 4</td>
</tr>
</tbody>
</table>

Table 3 Relation between the WBC counts and reaction

<table>
<thead>
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<th>Eosinophil counts/mm³</th>
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<th>Grade of reaction</th>
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<tbody>
<tr>
<td>&lt;1,000</td>
<td>4</td>
<td>1 3</td>
</tr>
<tr>
<td>1,000–2,000</td>
<td>12</td>
<td>2 3 5 2</td>
</tr>
<tr>
<td>2,000&lt;</td>
<td>13</td>
<td>2 2 9</td>
</tr>
</tbody>
</table>

Table 4 Relation between the eosinophil counts of peripheral blood and reaction

<table>
<thead>
<tr>
<th>Neutrophil counts/mm³</th>
<th>No. of case</th>
<th>Grade of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4,000</td>
<td>8</td>
<td>3 2 3</td>
</tr>
<tr>
<td>4,000–5,000</td>
<td>9</td>
<td>3 3 3</td>
</tr>
<tr>
<td>5,000&lt;</td>
<td>12</td>
<td>2 5 5</td>
</tr>
</tbody>
</table>

Table 5 Relation between the number of neutrophil counts of peripheral blood and reaction

<table>
<thead>
<tr>
<th>Lymphocyte counts/mm³</th>
<th>No. of case</th>
<th>Grade of reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2,000</td>
<td>10</td>
<td>1 4 5</td>
</tr>
<tr>
<td>2,000–3,000</td>
<td>10</td>
<td>1 2 4 3</td>
</tr>
<tr>
<td>3,000&lt;</td>
<td>9</td>
<td>2 2 3</td>
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Table 6 Relation between the number of lymphocyte counts of peripheral blood and reaction
4,250/mm³ with the mean of 1,970±900/mm³. Nine (69.2%) of 13 patients whose eosinophil counts were 2,000/mm³ or more showed severe reaction, while only 2 (12.5%) of 16 patients with eosinophils less than 2,000 showed severe reaction (Table 4; V=0.483, σ=0.120). A slight association with statistically significance between the severity of adverse reaction and the neutrophil counts was indicated (Table 5; V=0.428, σ=0.130). On the contrary, as seen in the Tables 6 (V=0.260, σ=0.150), there were no apparent relation between the severity of adverse reactions and lymphocyte counts.

The relation between the serum IgG levels of patients and the severity of reactions after DEC administration is shown in Figure 1. The average OD values±SD of no, mild, moderate and severe reaction groups were 0.76±0.30, 0.86±0.20, 1.03±0.20 and 1.25±0.20, respectively. The mean OD of 9 urban control sera in Guatemala was 0.18±0.09. Ten (90.9%) of 11 patients who experienced severe reaction (++) showed higher OD (over 1.0). Only one of five patients with mild reaction (+) showed higher OD. In two of three patients without reactions, OD was near 1.0. As the OD for the onchocerciasis specific IgG increased the severity of adverse reactions after DEC administration tended to increase.

**DISCUSSION**

Although there were some reports which dealt with the change of blood eosinophil counts after DEC treatment in the patients with onchocerciasis (Guerra-Caceres et al., 1980; Money, 1969), none of them described a relation between the severity of reactions elicited by DEC and eosinophil counts before treatment. In this study, we clarified that the patients with high eosinophils showed severe adverse reactions. Of four patients with the eosinophils less than 1,000/mm³, nobody showed

![Figure 1 Relation between O. volvulus-specific IgG and reaction.](image-url)
Severe reaction (¶¶). The eosinophil counts in blood is thus likely to be used in predicting the severe reactions in the patients with onchocerciasis following DEC administration. With regard to the role of eosinophil in filarial infection, Spry (1981) reported that the eosinophils released their granule products in response to the presence of microfilariae in the patients with filariasis, and these products could induce local or systemic reactions. In the tissues, the accumulation and degranulation of eosinophils occurred in patients with onchocerciasis around microfilariae or adult worm which were damaged by DEC treatment, and this could give rise to some of the clinical features of the Mazzotti reaction (Guerra-Caceres et al., 1980; Mimori, in press). By DEC treatment, neutrophil counts increased and the relation between clinical manifestations and neutrophils has been discussed (Henson et al., 1979; Sakamoto and Zea, 1983). In this study, a slight association with statistically significance between systemic complications and neutrophil counts was observed. However, lymphocyte counts in blood before DEC treatment were within normal level in most patients, and were not related to the severity of adverse reactions.

ELISA clarified the relation between the serum level of *O. volvulus*-specific IgG and the severity of adverse reaction. The higher the OD of serum samples, the higher was the severity of reactions. However, three patients with higher level of IgG did not show severe reactions. Various factors would be involved in these cases, such as anti-complement factors, poor antigenecity, acquisition of host antigen, immunotolerance and blocking antibodies (Henson et al., 1979). Greene et al. (1983) reported that very high pretreatment circulating immune complexes (CIC) levels were associated with an increase of ocular and systemic complications. The present study revealed that high eosinophil count in blood and/or high serum level of IgG were indicative laboratory data for severe adverse reactions caused by DEC treatment. A special precaution should be taken to treat such patients.

In the present study, the essential features of the clinical manifestations after DEC treatment were pruritus, rash, pain, lymphadenopathy and edema. The number of patients with pruritus, rash, pain, lymphadenopathy and edema reached the maximum at 24, 24, 24, 24 and 48 hours, respectively. The number of patients who complained of itching was decreased at 72 hours, while the other clinical manifestations remained stationary. Bryceson et al. (1977) reported that adverse reactions mentioned here appeared half an hour to 12 hours after DEC administration and continued for minutes, hours, or days.

Taylor et al. (1980) reported that pruritus appeared within 12 to 36 hours, the rash started between days 1 and 3 in most cases, lymphadenopathy and edema occurred between days 3 and 7. Our results observed are essentially similar to that of Taylor et al.

There are some reports which described that the severe reactions occurred in the patients with heavy infection of *O. volvulus* (Buck, 1974; Fuglsang and Anderson, 1974; Bryceson et al., 1977; Martinez and Tello, 1952). On the other hand, Greene et al. (1983) reported that pretreatment skin microfilaria counts showed a weak correlation with the total number of ocular and systemic complications after DEC treatment. Our study showed that six of 11 patients with high MFD experienced
severe reaction (¶¶), and as many as five out 13 patients with moderate and low MFD showed severe reactions. The patients with high MFD tended to show severe reactions, although some of the patients with low or moderate MFD showed severe reaction. This finding suggests that the number of eosinophil counts, serum immunoglobulin level such as IgG and IgE and the circulating immune complexes are more important factors than MFD, which predict severe adverse reactions by DEC administration.

ACKNOWLEDGMENT

This study was supported by the Overseas Scientific Research Grants No. 57041041 from the Ministry of Education of Japan. We wish to thank Dr. H. A. Gody, Director de Servicio Nacional de Erradicacion de la Malaria, Ministerio de Salud Publica, Guatemala, and his colleagues for their kind cooperation. We also highly appreciate Dr. T. Suzuki, JICA, for his encouragement and Dra. Marianonieta of Amatitlan Nacional Hospital for the kind cooperation.

Appreciation is also expressed to Dr. T. Yoshimura, University of Occupational and Environmental Health, Kitakyushu, Japan, for his helpful criticism and suggestions in the preparation of the manuscript.

REFERENCES

11) Martinez, B. M. and Tello, P. R. (1952): Modificacionnes en la eosinofilia de los oncocercosos


Diethylcarbamazine 治療時におけるオンセルカ症患者の臨床像と
治療前検査成績の関係について

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Zea, G. F.・Castro, J. C.

中米グアテマラ国オンセルカ症患者29名について DEC (5mg/kg/day 7日間) で治療し、その時における臨床像の観察と治療前における検査成績より、治療時における臨床像の重症度を予測した。治療時の主な反応は発熱、発疹、発赤、リンパ節腫脹、浮腫であった。これらは DEC 投与による炎症性反応であると考えられた。これら炎症性反応の重症度と治療前の検査成績の関係において末梢血中の好酸球及び O. volvulus-antigen specific IgG との間に強い相関がみられ、治療上これらの成績の高い患者には充分な注意が必要と考えられた。