Triethylene-Tetramine (Trien) Therapy for Wilson’s Disease

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Triethylene-tetramine (trien), in increasing dose from 1.0-2.0 g/day to 2.5-3.0 g/day, was used for 4 Japanese patients with Wilson’s disease who were intolerant of D-penicillamine (D-PC). Before the treatment, urinary copper excretion (UCE) was 70-96 μg/day. UCE increased to 1,512-2,352 μg/day on the day of initial administration, and remained at levels between 350-1,100 μg/day, thereafter. During 2 months of trien therapy, neurological deficits regressed in three patients, and only slightly in one patient. No adverse effects were observed. These results and the retrospective survey on 17 patients treated with D-PC confirmed that trien is less potent but a safer copper chelating agent than D-PC. The transient aggravation of neurological deficits seen in two patients during the early stage of the treatment suggested that trien, as D-PC, should be started in small doses and gradually increased.

Wilson’s disease (WD), an autosomal recessive disorder of copper metabolism, is characterized by neurologic and psychiatric impairments as well as hepatic, renal, articular and ocular abnormalities, resulting from excessive copper accumulation in the central nervous system and other organs. D-Penicillamine (D-PC) has been a standard therapeutic drug for WD (Walshe 1956; Sternlieb and Scheinberg 1964). However, it has also several adverse effects which may appear in 10-30% of D-PC treated patients, and 10% of the patients with WD cannot tolerate longterm D-PC therapy (Haggstrom et al. 1980; Walshe 1982). In 1969,
Walshe introduced a new chelating agent; triethylenetetramine dihydrochloride (tren or trien) for treatment of D-PC intolerant patients with WD. Subsequent clinical trials indicated that trien is effective for WD, and less toxic than D-PC (Walshe 1982; Scheinberg et al. 1987). In the United States, trien is now commercially available as an acceptable alternative for D-PC (Klaassen 1990). In Japan, however, trien therapy for WD has been tried sporadically in a few institutes (Arashima et al. 1989; Yamamura et al. 1990). Here we report the results of trien therapy for 4 Japanese patients intolerant of D-PC, and discuss the copper chelating effects as well as side effects of trien and D-PC.

**Patients and Methods**

The subjects were 4 patients with WD, in whom initially D-PC was administered but discontinued because of aggravation of leukopenia or other adverse effects of D-PC. All patients had various degree of neurological and psychiatric impairments, liver cirrhosis and Kayser-Fleisher ring, as well as low levels of serum copper and coeruloplasmin, and high basal levels of urinary copper excretion.

Trien (Wako Pure Chemical Industry, Osaka) was purified, neutralized and was crystalized according to the method described by Dixon et al. (1972). It was then divided into packages of 0.5 g each by the Department of Pharmaceutical Sciences of Tohoku University Hospital. Initially, 1.0-2.0 g/day of trien was orally administered into the empty stomach. The dose was subsequently increased to 2.5-3.0 g/day. Informed consents were obtained from patients or from their parents. In some cases the following medications were also given; levo-dopa, amantadine, clonazepam, mercaptopropionyl-glycine, or adenoine.

Therapeutic effects of trien were evaluated by neurological assessments and by the measurements of urinary copper levels before and after the initiation of trien therapy. Laboratory examinations were repeated regularly. Furthermore, after reviewing the medical records of 17 patients treated by D-PC in the Department of Neurology, the cupruretic action as well as adverse effects of the two drugs were compared.

**Case History**

*Case 1.* A 43-year-old woman was referred to our hospital because of the extremital involuntary movements and gait disturbance. Her parents were of consanguinous marriage. She suffered from nephritis at the age of 13. She often had subcutaneous hemorrhages after very minor trauma.

Since the age of 41, she developed tremulous involuntary movements of the upper limbs, which gradually extended to the jaw and to the lower limbs. The gait became difficult. She was admitted to a local hospital and diagnosed as WD. D-PC, 800 mg/day, was given, but discontinued within two weeks because of aphtha and oro-pharyngeal pain. These symptoms disappeared shortly after D-PC withdrawal, but neurological symptoms aggravated. Six months later, she was admitted to our hospital, and was initially given 1.0 g/day of trien which was subsequently increased to 2.5 g/day.

*Case 2.* A 39-year-old woman was admitted to our hospital because of hemorrhagic tendency and coarse involuntary movements of the extremities which had appeared 3 years previously. The upper limbs showed typical wing-beating tremor on volitional movements, especially on arm extension. The lower limbs showed coarse abduction-adduction tremor of the thighs on knee flexion in the supine position. She was diagnosed as WD, and D-PC was given with increasing dose from 200 mg to 600 mg daily. The peripheral leukocytes (WBC) count which was 2,100/mm³ before D-PC decreased to 1,600/mm³ three weeks later, and to
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1,300/mm³ after four weeks. D-PC was discontinued. Three months later, 1.5 g/day of trien was administered at first, and was increased subsequently to 3.0 g/day.

Case 3. A 36-year-old man was admitted to our hospital because of gait disturbance. At the age of 28, he developed anthropic tendency followed by euphoric and childish behaviors with delusion of grandeur. He was treated in a psychiatric hospital. During this period, duodenal ulcer recurred and liver cirrhosis was found. Since the age of 33, he had difficulties in writing and speech, clumsiness of left extremities followed by slowness of movement and short-steppage gait. In 1984, he was diagnosed as WD, and treated with D-PC, 300 mg/day. After admission to our hospital, D-PC was increased to 600 mg/day. His WBC count which was 2,600–3,000/mm³ on admission fell to 2,300/mm³. D-PC was replaced by 0.16–0.18 g/day of dimercaprol (BAL) without sufficient cupruresis. Then, BAL was replaced by 1.5 g/day of trien which was later increased to 2.5 g/day.

Case 4. A 17-year-old man was admitted to our hospital because of incomprehensiveness in speech and illegible small writing which had appeared at the age of 14. Neurological examinations revealed severe dysphonia, micrographia, and fine postural finger tremor. He was diagnosed as WD, and 300 mg/day of D-PC was given. Several days after the dose was increased to 600 mg/day, his WBC count which was 3,300/mm³ before D-PC administration fell to 2,800/mm³. D-PC was discontinued. Four days later, 2.0 g/day of trien was given and subsequently increased to 3.0 g/day.

RESULTS

Since the first day of trien therapy, urinary copper excretion (UCE) showed

<table>
<thead>
<tr>
<th>Casea</th>
<th>Age &amp; Sexb</th>
<th>Age of onsetc</th>
<th>A: UCE Befored (µg/day)</th>
<th>B: UCE First day (µg/day)</th>
<th>B/A</th>
<th>Dose of drug (g/day)</th>
<th>C: UCE 1 month (µg/day)</th>
<th>C/A</th>
<th>Dose of drug (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-1</td>
<td>17 F</td>
<td>14</td>
<td>170 (3)</td>
<td>3145</td>
<td>18.5</td>
<td>1.2</td>
<td>1560</td>
<td>9.2</td>
<td>1.2</td>
</tr>
<tr>
<td>P-2</td>
<td>18 M</td>
<td>17</td>
<td>270 (6)</td>
<td>4968</td>
<td>18.4</td>
<td>0.6</td>
<td>2850</td>
<td>10.5</td>
<td>1.2</td>
</tr>
<tr>
<td>P-3</td>
<td>17 M</td>
<td>14</td>
<td>155 (3)</td>
<td>2635</td>
<td>17.0</td>
<td>0.6</td>
<td>2770</td>
<td>17.8</td>
<td>0.6</td>
</tr>
<tr>
<td>P-4</td>
<td>16 M</td>
<td>14</td>
<td>247 (1)</td>
<td>1615</td>
<td>6.6</td>
<td>0.6</td>
<td>1653</td>
<td>7.0</td>
<td>1.2</td>
</tr>
<tr>
<td>P-5</td>
<td>23 M</td>
<td>21</td>
<td>95 (3)</td>
<td>504</td>
<td>5.3</td>
<td>0.6</td>
<td>947</td>
<td>10.0</td>
<td>0.8</td>
</tr>
<tr>
<td>P-6</td>
<td>18 M</td>
<td>17</td>
<td>256 (3)</td>
<td>717</td>
<td>2.8</td>
<td>0.6</td>
<td>707</td>
<td>2.8</td>
<td>0.8</td>
</tr>
<tr>
<td>P-7</td>
<td>20 M</td>
<td>15</td>
<td>113 (4)</td>
<td>622</td>
<td>5.5</td>
<td>0.2</td>
<td>1650</td>
<td>14.6</td>
<td>0.6</td>
</tr>
<tr>
<td>P-8</td>
<td>39 F</td>
<td>37</td>
<td>185 (2)</td>
<td>814</td>
<td>4.4</td>
<td>0.2</td>
<td>1412</td>
<td>7.6</td>
<td>0.6</td>
</tr>
<tr>
<td>T-1</td>
<td>43 F</td>
<td>40</td>
<td>70 (2)</td>
<td>1512</td>
<td>21.9</td>
<td>1.0</td>
<td>390</td>
<td>5.5</td>
<td>2.5</td>
</tr>
<tr>
<td>T-2</td>
<td>39 F</td>
<td>37</td>
<td>88 (1)</td>
<td>1223</td>
<td>13.9</td>
<td>1.5</td>
<td>1080</td>
<td>12.3</td>
<td>3.0</td>
</tr>
<tr>
<td>T-3</td>
<td>36 M</td>
<td>28</td>
<td>567 (1)</td>
<td>2160</td>
<td>3.8</td>
<td>1.5</td>
<td>688</td>
<td>1.2</td>
<td>2.5</td>
</tr>
<tr>
<td>T-4</td>
<td>17 M</td>
<td>14</td>
<td>96 (1)</td>
<td>2352</td>
<td>24.5</td>
<td>2.0</td>
<td>819</td>
<td>8.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

aNote that Case P-8 and Case T-2 are one and the same patient.
bF, female; M, male.
cAge at onset of neurological or psychiatric symptoms.
dUCE of one day or the mean UCE of several days (in parenthesis) before trien therapy.
eUCE with 0.18 mg of dimercaprol administration.
a steep increase to more than 1.0 mg/day in case 1 and 3, and to more than 2.0 mg/day in Cases 2 and 4. Then, it decreased fairly rapidly to the level of 0.5–1.3 mg/day. The increased dose resulted in a slight elevation of UCE. More than a month after the initiation of trien therapy, 0.3–1.0 mg/day of UCE was obtained by daily administration of trien, 2.5–3.0 g/day (Table 1 and Fig. 1). Neurological symptoms and signs apparently regressed in Cases 1, 2 and 3, and only slightly in Cases 4. During two months or more of trien therapy (maximum: three years), no adverse effects were seen, apart from mild and transient numbness of lips in Case 1. In particular, no aggravation of leukopenia, the main cause of D-PC discontinuation in Cases 2–4, was observed. In Cases 1 and 4, however, transient deterioration of tremor or micrographia was seen during the first 2–4 weeks of trien therapy.

Fig. 1. Trien therapy and urinary copper excretion in 4 patients with Wilson's disease. ○, days without chelating agent; ●, days with chelating agents; B, dimercaprol (BAL); T, trien; *, alternating administration of 1.0 g/day and 1.5 g/day; **administration on every other day. Numerals on the top were daily dose (g/day).
The retrospective survey on the clinical records of the 17 WD-patients treated with D-PC, suggested the following adverse effects of D-PC, aggravation of leukopenia in 7 cases, nausea, vomiting, diarrhea or abdominal pain in 5, generalized skin-rash in 1, and aphtha and oro-pharyngeal pain in 1 patient. Trien at the dose of 400–800 mg/day was given when the patients developed these side effects. Transient aggravation of neurological deficits was suspected in 10 patients. In 8 of the 17 patients, D-PC was continued for more than a month under UCE measurement. UCE levels in these patients were compared with the results of the present trien therapy (Table 1). UCE without chelating agents were significantly lower in patients treated with trien (Case T-1, T-2 and T-4 in Table 1, \( p < 0.01 \), Student's t-test). Though the initial dose of D-PC and trien varied largely in each patient, UCE on the first day of treatment showed no significant differences in two groups. A month after the initiation of treatment, patients treated with trien showed lower UCE than those treated with D-PC (\( p < 0.05 \)).

**DISCUSSION**

Due to its potent copper chelating action, D-PC has been the first choice for the treatment of WD (Walshe 1956; Sternlieb and Scheinberg 1964), but it also causes several side effects; fever, suppression of hematopoetic system, hypersensitive skin rash, nephrotic syndrome, and others (Adams et al. 1964; Corcos et al. 1964; Sternlieb and Scheinberg 1964; Walshe 1969; Bird 1974; Scheinberg et al. 1987). Though most patients can be treated effectively with D-PC, its side effects may require dose-reduction or complete withdrawal of D-PC in about 10% of patients (Walshe 1982). In our retrospective survey on D-PC therapy, only 9 of the 17 patients could endure continuous D-PC therapy, and 7 of other remaining 8 patients were intolerant because of aggravation of pre-existing leukopenia.

In 1969, Walshe introduced trien therapy for WD-patients with D-PC induced nephropathy. Subsequent clinical experiences showed that trien is effective for patients intolerant of D-PC (Walshe 1982; Scheinberg et al. 1987; Klaassen 1990; Yamamura et al. 1990). The comparison of the present results and the retrospective survey on patients treated with D-PC showed that both drugs induced an increase in UCE during the initial several days. Thereafter, however, the patients treated with trien showed lower levels of UCE than the patients treated with D-PC. Walshe (1973) reported similar observations. The difference in our study should be carefully interpreted, because the patients treated with D-PC were de novo, and those treated with trien had been previously treated with D-PC. Still, trien appeared less potent in copper chelating action than D-PC. Neurologically, however, 3 of our 4 patients improved after trien therapy, while the remainder did only slightly. All patients tolerated trien administration well for more than 2 months without apparent side effects. It should be stressed, in particular, that aggravation of leukopenia, the main cause...
of D-PC withdrawal in 3 patients, was not observed. Walshe (1982) and Scheinberg et al. (1987) reported that sufficient therapeutic results could be obtained by long term administration of trien alone, without apparent side effects except for slight iron-deficient amenia in female patients. The discontinuation of D-PC in patients with WD results in a rapid clinical deterioration, which is often fatal, but the replacement of D-PC with trien may prevent this adverse clinical course (Scheinberg et al. 1987). Despite the small number of patients, our trial confirmed the previous observations that trien is a safe and effective therapeutic agent for patients with WD. The problem of its lesser potency in copper chelating action might be solved by simultaneous administration of zinc sulfate which induces copper excretion via the stools (Brewer et al. 1983; Hoogenraad et al. 1987).

During the initial treatment of WD with D-PC, neurological deteriorations often develop. They are usually transient but may also be permanent (Sternlieb and Scheinberg 1964; Deiss et al. 1971; Brewer et al. 1987). According to Brewer et al. (1987), the copper mobilized by D-PC from a large store of hepatic copper may be excreted into the urine on one hand, and may be newly deposited in the central nervous system on the other, the latter causing neurological deterioration. In the present trial, two patients showed transient neurological aggravation shortly after the initiation of trien therapy, which has not been reported. Though it has been suggested that trien and D-PC may mobilize copper from different body compartment (Walshe 1973), the present observations supported a hypothesis by Brewer et al. (1987) that trien may also show the syndrome of initial neurological worsening. Thus, trien as D-PC should be first given in small doses and then gradually increased to avoid or mitigate abrupt copper mobilization and neurological deteriorations.

Though a majority of adverse effects of D-PC occur mostly during first 4 weeks of treatment, others such as nephrotic syndrome may develop after several months or years of D-PC therapy (Sternlieb and Scheinberg 1964; Walshe 1969; Arashima et al. 1989; Yamamura et al. 1990). WD is a rare disorder, but the patients have to take medications through life. Therefore, as for trien therapy, too, an accumulation of therapeutic experiences even on a few patients, together with long-term investigations on possible side effects, is indispensable to establish better therapeutic schedules for WD. We hope that the present observations on 4 Japanese patients with WD may provide additional data to facilitate authorized release of trien in nations including Japan where trien is still an investigative drug.

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References


