Dapsone Treatment of Pneumocystis carinii Pneumonia in the Acquired Immunodeficiency Syndrome

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All patients with the acquired immunodeficiency syndrome treated for their first episode of Pneumocystis carinii pneumonia at San Francisco General Hospital between 1 April 1985 and 15 July 1985 were evaluated for their response to treatment with dapsone (100 mg/day) by mouth for 21 days. Of 44 patients evaluated, 18 were eligible for the study. Of these 18 patients, the conditions of 7 of them worsened or failed to improve during treatment with dapsone and they were considered treatment failures. These patients were changed to standard therapy after 4 to 8 days of dapsone therapy. The remaining 11 patients (61%) improved within 3 to 10 days after dapsone therapy was started. Side effects of dapsone therapy were noted in 6 of 11 patients (of these 11 patients, 5 had a rash, 1 had a rash and abnormal liver enzymes, and 1 had abnormal liver enzymes), but in none of the patients were these side effects severe enough to require the cessation of medication. Based on comparison with historical controls, oral dapsone therapy alone appeared to be less effective than standard therapy or the combination of dapsone plus trimethoprim for P. carinii pneumonia in patients with acquired immunodeficiency syndrome.

Pneumocystis carinii pneumonia is the most common index diagnosis in patients with the acquired immunodeficiency syndrome (AIDS) (5). Currently, there are two approved treatments: trimethoprim-sulfamethoxazole and pentamidine isethionate (10, 14; N. C. Klein, F. P. Ducanson, T. H. Lenox, C. Forszpaniak, C. Scherer, H. Quentzel, and G. P. Wormser, Proc. 2nd Int. Conf. on AIDS, abstr. no. 293, 1986). With either regimen, approximately 50% of patients develop major toxic responses necessitating a change in therapy (1, 8, 9, 12, 14; Klein et al., Proc. 2nd Int. Conf. on AIDS, 1986); response rates are equivalent for the two regimens (10, 15; Klein et al., Proc. 2nd Int. Conf. on AIDS, 1986). Using the rat model of P. carinii pneumonia, Hughes and Smith (11) showed that dapsone (5 mg/kg per day) with trimethoprim (60 mg/kg per day) or dapsone alone (25 mg/kg per day) were at least as effective as standard doses of trimethoprim-sulfamethoxazole. In a recent open study from the San Francisco General Hospital in patients with AIDS experiencing their first episode of P. carinii pneumonia, oral therapy with the combination of dapsone (100 mg, or about 2 mg/kg, per day) with trimethoprim (20 mg/kg per day) was both well tolerated and effective (13). A subsequent randomized, placebo-controlled trial in which dapsone-trimethoprim was compared with trimethoprim-sulfamethoxazole showed that dapsone-trimethoprim was as effective and less toxic than trimethoprim-sulfamethoxazole (3, 4, 6). During therapy the patients underwent a daily history and physical examination and were assessed for dyspnea (13, 14). A complete blood count and serum chemistries

MATERIALS AND METHODS

All AIDS patients 18 years or older with their first episode of P. carinii pneumonia diagnosed at San Francisco General Hospital between 1 April 1985 and 5 July 1985 were evaluated for inclusion in this study. For diagnosis, sputum from all patients was examined; sputum was induced by inhalation of hypertonic saline (3). If P. carinii was not found in induced sputum, the patient underwent bronchoscopic evaluation (bronchoalveolar lavage and transbronchial biopsy) as described previously (4, 6). All the patients that were treated had microscopically confirmed P. carinii pneumonia. Patients were excluded from the study for the following reasons: (i) history of hypersensitivity to dapsone, (ii) abnormal glucose-6-phosphate-dehydrogenase (Qualitative Screening procedure; Sigma Chemical Co., St. Louis, Mo.), (iii) creatinine greater than 2 mg/dl, (iv) total neutrophil count less than 1,000/μl, (v) platelet count less than 100,000/μl, (vi) more than 48 h of other therapy for P. carinii pneumonia, and (vii) predicted survival of less than 1 week without therapy. These were the same exclusion criteria applied in our prior study (13) of dapsone-trimethoprim therapy.

The study protocol and consent form were approved by the Committee on Human Research of the University of California, San Francisco, an Institutional Review Board constituted according to U.S. Food and Drug Administration guidelines.

After participants in the study gave informed consent, an initial history was taken and a physical examination was performed by one of the investigators. Results of other initial and follow-up studies are given in Tables 1 and 2. At the end of therapy, the procedure that established the original diagnosis (sputum induction or bronchoalveolar lavage) was repeated, and the specimens were examined for P. carinii (3, 4, 6). During therapy the patients underwent a daily history and physical examination and were assessed for dyspnea (13, 14). A complete blood count and serum chemistries

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TABLE 1. Comparison of pretherapy variables and treatment outcome in study patients

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Total no. of subjects</th>
<th>Pretreatment findings</th>
<th>Value (or mean value)</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18</td>
<td>Arterial pO&lt;sub&gt;2&lt;/sub&gt; (mm Hg [Pa])</td>
<td>73.8 (9,838)</td>
<td>68.5</td>
</tr>
<tr>
<td>Historical controls</td>
<td></td>
<td>DLCO (% predicted)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone-trimethoprim&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15</td>
<td>68.5 (9,131)</td>
<td>56.9</td>
<td>52.3</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole or pentamidine&lt;sup&gt;f&lt;/sup&gt;</td>
<td>40</td>
<td>66.5 (8,864)</td>
<td>58.5</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Uptake score of 0 (none) to 3 (greater than liver) (14).

<sup>b</sup> Results have been described previously (13).

<sup>c</sup> Results have been described previously (14).

Some adverse reactions were performed every 3 days; and methemoglobin saturation levels, chest radiographs, and arterial blood gases were obtained every 7 days. Pulmonary function testing and lung gallium scans were performed as described previously (13, 14).

Patients who failed to respond to dapsone alone were switched to alternate therapy because of clinical failure after a mean of 5.8 days (range, 4 to 8 days) of therapy (Table 1). Of these patients, 8 received trimethoprim-sulfamethoxazole by the attending physician, even though the protocol of this study specified pentamidine. The mean initial arterial pO<sub>2</sub> of the treatment failures was 63.4 mm Hg (8,451 Pa) versus 84 mm Hg (11,197 Pa) for the patients completing therapy with dapsone (P < 0.001). The remaining 11 patients showed subjective or objective improvement in 3 to 10 days (mean, 6.8 days), as assessed by reduction in dyspnea score and respiratory rate, and temperature; and they completed treatment successfully. The response rate to dapsone therapy was significantly decreased as compared with historical controls treated with either dapsone-trimethoprim (15 of 15 patients; P = 0.007) (13) or trimethoprim-sulfamethoxazole or pentamidine (34 of 40 patients; P = 0.05) (14).

The patients who failed to respond to dapsone therapy could be differentiated from those who improved by respiratory rate measurements. The mean initial respiratory rate in the responders was 22/min; this fell to 19.5/min by day 6 and to 17/min by the end of therapy. The initial mean respiratory rate in the patients who failed therapy was 26/min, and this rose to 35/min by day 6 of therapy.

Of 18 patients, 3 (17%) died during the treatment period. The first of these patients had progressive respiratory distress and died after 5 days of therapy with dapsone, 9 days of therapy with trimethoprim-sulfamethoxazole, and 15 days of therapy with pentamidine. Postmortem examination showed P. carinii in the lungs and disseminated cytomegalovirus (CMV) infection. The other two patients died of respiratory failure after 3 to 4 days of dapsone therapy and 8 to 10 days of pentamidine therapy; autopsies were not performed.
TABLE 2. Comparison of posttherapy variables in patients completing treatment with the study drug

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of subjects studied</th>
<th>Arterial pO₂ (mm Hg [Pa])</th>
<th>DLCO (% predicted)</th>
<th>Vital capacity (% predicted)*</th>
<th>Lung gallium uptake (0–3)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone</td>
<td>11</td>
<td>82.5 (10,997)</td>
<td>69.9</td>
<td>68.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Historical controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone-trimethoprim</td>
<td>13</td>
<td>88.7 (11,824)</td>
<td>62.3</td>
<td>78</td>
<td>1.0</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole or pentamidine</td>
<td>34</td>
<td>86.5 (11,530)</td>
<td>62.5</td>
<td>78</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* P = 0.05 for the dapsone treatment regimen alone compared with other treatment regimens.

Results have been described previously (13).

Cultures for CMV were performed on induced sputum or bronchoalveolar lavage in seven patients. All three patients who died had CMV in induced sputum; however, three additional patients had CMV in sputum and recovered uneventfully. One additional patient had a negative CMV culture but failed to improve on dapsone therapy and was switched to trimethoprim-sulfamethoxazole therapy.

Of the 11 patients who completed 21 days of therapy, all but 3 had improvement in their DLCO; 7 of the 11 had decreased $^{67}$Ga uptake, while 4 had unchanged $^{67}$Ga uptake. The results of the pulmonary function studies, $^{67}$Ga scan, and arterial pO₂ after standard therapy (14) or dapsone-trimethoprim therapy (13) compared with those obtained after dapsone therapy alone are given in Table 2.

Of the 11 patients who completed 21 days of therapy, 6 had adverse effects from dapsone. Five patients developed an erythematous maculopapular rash between days 9 and 12. All five of these patients continued to receive dapsone at an unchanged dosage and received diphenhydramine orally without progression of the rash; the rash disappeared within 3 days in every case. Six patients had a decrease in hematocrit of 5 to 10% (mean drop, 6.7%), which occurred in all six patients after the first week of treatment; none of the patients required a transfusion. Studies to document the mechanism of decline in hematocrit were not performed. Two patients had methemoglobinemia ranging between 5 and 8% during the second week of treatment; the methemoglobin saturations dropped to <5% during the third week. One patient had elevation of serum aspartate and alanine aminotransferase to greater than 100 U/dl (2 to 3 times the upper limit of normal); the elevation occurred at the end of the second week of therapy, and the values returned to normal 2 days after the completion of treatment. No patient developed neutropenia, thrombocytopenia, or elevation of serum creatinine; and nausea or vomiting did not occur.

Of the 11 patients who responded to dapsone therapy, 10 were diagnosed with *P. carinii* by sputum induction, and the procedure was repeated at the end of therapy; *P. carinii* was present in only one patient. Repeat bronchoalveolar lavage in one patient initially diagnosed by lavage showed persistent *P. carinii* as has been described previously by standard chemotherapeutic regimens (2, 7, 13, 14).

**DISCUSSION**

Based on comparisons with historical controls who were also treated at this hospital, dapsone (100 mg/day) given orally was less effective than dapsone-trimethoprim, trimethoprim-sulfamethoxazole, or pentamidine for the treatment of *P. carinii* infections in patients with AIDS. The observed 61% initial response rate (95% confidence limits, 38.5 to 83.5%) was worse than the values noted in previous studies of dapsone-trimethoprim (100% efficacy) (13) and trimethoprim-sulfamethoxazole or pentamidine (85% efficacy) (14). The patient populations were similar in the three studies, the only significant difference being that the initial DLCO was better in the group that received dapsone than in the groups that received other drugs (Table 1). Thus, patients given dapsone were, if anything, less ill than those given the other drugs, and hence, the suboptimal efficacy of dapsone cannot be attributed to differences in the patient population.

Because our historically controlled data suggest that dapsone alone is less effective than dapsone-trimethoprim, trimethoprim-sulfamethoxazole, or pentamidine for the treatment of *P. carinii* pneumonia in patients with AIDS, future randomized prospective comparisons of dapsone therapy with these standard chemotherapeutic regimens should be carefully designed and should incorporate sequential data analysis. For the same reason, we do not generally recommend dapsone alone as the first-line therapy for *P. carinii* pneumonia. However, as dapsone appeared to be less toxic than standard treatment regimens, it may be useful for chemoprophylaxis or as an alternative treatment regimen for certain patients, such as those with major adverse reactions to other forms of therapy.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


