Eflornithine Treatment of Refractory Pneumocystis carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome*

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Eflornithine was offered as compassionate treatment of 33 episodes of Pneumocystis carinii pneumonia in 31 patients with acquired immunodeficiency syndrome who were intolerant of and/or unresponsive to conventional trimethoprim-sulfamethoxazole or pentamidine therapy. A full course of eflornithine consisted of ten days at 400 mg/kg/d but no more than 30 g/d in four divided intravenous doses, four days at 300 mg/kg/d in four divided intravenous doses, and then up to six weeks at 300 mg/kg/d in four divided oral doses where tolerated. Of 33 patient-episodes, 15 patients were discharged from the hospital without need for supplemental oxygen after receiving ten or more days of parenteral therapy and were classified as responders. Of the 16 episodes classified as treatment failures, death occurred within the first 10 days of therapy in 12, and supplemental oxygen could not be withdrawn in 4. The other two patients left the hospital without need of oxygen after receiving one and six days of treatment with eflornithine and were not considered evaluable for efficacy. The most serious adverse effect was thrombocytopenia, which occurred in 12 of 19 patients treated for ten days or more. Serious bleeding associated with thrombocytopenia was observed in two patients. Other common adverse effects were anorexia, nausea, and diarrhea. Prior to receiving eflornithine, 13 of 15 responders had received ten or more days of conventional therapy without demonstrating clinical improvement. Two had improved while receiving conventional therapy but were switched to eflornithine because of a treatment-limiting adverse effect of standard therapy. These results suggest that eflornithine may be useful as an alternative therapeutic agent for Pneumocystis carinii pneumonia. Studies designed to determine proper dosage, duration of therapy, and efficacy as primary therapy are warranted.

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Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS). It occurs in up to 80 percent of patients with a mortality of greater than 20 percent. The conventional drug treatments for PCP, trimethoprim-sulfamethoxazole (TS) and pentamidine (PTM), are generally considered equally effective, but 20 to 40 percent of patients fail to respond. In addition, these drugs have a 50 to 60 percent incidence of adverse reactions, which frequently limit treatment. Thus, there exists a need for alternative agents that have similar or more favorable efficacy and toxicity characteristics.

Eflornithine hydrochloride (DL-alpha-fluoromethylornithine hydrochloride monohydrate) may prove to be such an alternative agent. Its mechanism of action is attributed to irreversible binding with ornithine decarboxylase, a key enzyme in the biosynthesis of the intracellular polyamines, putrescine, spermine, and spermidine. These polyamines are essential for the growth and multiplication of all eukaryotic cells. By inactivating ornithine decarboxylase and blocking the biosynthesis of polyamines, eflornithine inhibits the growth of the P. carinii organism. Eflornithine has been successfully used to treat patients with African trypanosomiasis, and recent reports have supported its role in the treatment of PCP in patients with AIDS.

This article describes the efficacy and safety of eflornithine administered under a compassionate-use protocol for treating PCP in AIDS patients who were intolerant of or unresponsive to conventional therapy.

AIDS = acquired immunodeficiency syndrome; PCP = Pneumocystis carinii pneumonia; PTM = pentamidine; TS = trimethoprim-sulfamethoxazole
Patients and Methods

Patients

Hospitalized patients requiring treatment for PCP were enrolled in the compassionate-use protocol if they met the following criteria at the time of entry: (1) membership in an AIDS high-risk group based on Centers for Disease Control (1982) criteria; (2) presence of dyspnea requiring oxygen therapy accompanied by other clinical signs and symptoms of pneumonitis; (3) identification of P carinii organisms from appropriate sites of secretions or lung tissue obtained by bronchoscopy prior to the time of entry; (4) treatment failure or treatment-limiting adverse reaction to conventional treatment with TS or PTM or both or recurrence of PCP in a patient who had responded to compassionate use of efloornithine during a previous episode of PCP; and (5) ability to provide an informed consent.

Definitions

Treatment failure was defined as lack of clinical improvement after five or more days of treatment with conventional agents. Clinical improvement meant that the need for supplemental oxygen therapy was reduced compared with the initial 24-h period of therapy; the F1O2 requirement was less than 0.40; and there was no worsening of fever, cough, or adventitious sounds.

Exclusions

Patients were excluded from the study for any of the following reasons: (1) age younger than 18 or older than 60 years of age; (2) pregnancy; (3) significant renal impairment (estimated creatinine clearance less than 20 ml/min/72 kg of body weight); (4) serum transaminase levels above 400 IU; (5) granulocyte count below 1,500/cu mm; or (6) platelet count below 75,000/cu mm. The inclusion criterion for platelet count was increased to 150,000/cu mm during the course of the study.

Dosage and Administration

Efloornithine therapy was begun at 400 mg/kg/d (up to a maximum dose of 30 g/d) in four divided intravenous piggyback infusions every 6 h for 10 days. This was followed by 75 percent of the initial dose given in the same manner for four additional days. After completion of 14 days of parenteral treatment, efloornithine was continued with use of an oral solution at a dose of 75 mg/kg every 6 h for an additional four to six weeks, provided that patients were willing to comply and that there were no intervening adverse events.

The initial efloornithine dosage was reduced for patients with mild to moderate renal insufficiency as follows: 25 percent reduction if the serum creatinine concentration was 1.5 to 2.5 mg/dl and 50 percent reduction if the concentration was 2.5 to 3.0 mg/dl. Treatment was interrupted or terminated for occurrence of drug-related adverse reactions or whenever thrombocytopenia or granulocytopenia counts decreased to 50,000/cu mm or 500/cu mm, respectively. The toxicity end point for platelet counts was increased by the investigators to 100,000/cu mm during the course of the study. Therapy was reinitiated at no more than half of the interrupted dosage provided that further treatment was indicated and the affected laboratory values had returned to normal.

The study protocol was reviewed and approved by the Committee for Human Research of the University of Southern California School of Medicine.

Evaluation of Efficacy

Patients were classified as responders if they completed at least ten days of parenteral efloornithine therapy, were discharged without need for supplemental oxygen, and were free of recurrence for at least three months following completion of parenteral efloornithine. Patients who died before completing ten days of parenteral therapy or who continued to require oxygen therapy after ten or more days of parenteral efloornithine were classified as treatment failures.

Evaluation of Adverse Effects

Patients were evaluated for occurrence of adverse effects throughout the course of their inpatient parenteral therapy and then at biweekly intervals during oral therapy. Laboratory studies (serum chemistry evaluations, complete blood cell counts, platelet counts) were done every two days during parenteral treatment and at each biweekly visit during oral therapy.

Thrombocytopenia was considered a complication of therapy if the platelet count fell below 100,000/cu mm, with an absolute fall of at least 50,000/cu mm below pretreatment values. Leukopenia was considered a complication if the leucocyte count fell below 2,000/cu mm, with an absolute fall of at least 1,000/cu mm during therapy. Anemia was considered a complication if the hematocrit fell below 10 g/dl, with an absolute fall of at least 3 g/dl.

Pure-tone audiometric studies (250 to 8,000 cps) were done at initiation of therapy in some patients who were able to cooperate and in those who returned complaining of hearing difficulty after completion of therapy. Hearing loss was considered an adverse effect if (1) no pretherapy audiogram was done, but the patient complained of hearing loss, and an audiogram demonstrated hearing impairment after treatment; or (2) comparison of pre- and post-treatment audiograms showed a 20 dB or greater increase in hearing threshold at one or more tested frequencies.

Statistical Analysis

Results are reported as mean ± SD unless otherwise indicated. The Wilk-Shapiro test was used to assess the normality of distributions. For normal distributions, differences in means were examined by using t tests. For nonnormal distributions, differences in medians were examined by using Wilcoxon rank-sum tests. Differences in proportions were analyzed by using Fisher exact probability tests. All tests were two tailed, and a significance level of 0.05 was used to detect differences and associations.

Results

Patients

Thirty-one patients received efloornithine because they were unresponsive to or intolerant of TS or PTM or both. Two patients received a second course of efloornithine as initial therapy for PCP after responding to efloornithine treatment of a previous episode. Characteristics of these 33 patients (1 woman and 30 men) over the total of 33 patient-episodes are summarized in Table 1. Average age was 35.7 ± 8.4 years (range, 23 to 55 years). Average weight was 65.3 ± 9.8 kg (range, 43.0 to 88.5 kg), representing 88.3 ± 9.0 percent (range, 55 to 100 percent) of reported usual weight. Prior to initiation of efloornithine, conventional therapy had been administered for 10.4 ± 4.9 days (range, 0 to 24 days). The entry arterial to alveolar oxygen tension ratio (PaO2/PaO2) was 0.54 ± 0.20 (range, 0.08 to 0.83). The treated episode of PCP was the first episode in 26 of 33 patient-episodes and the second or third episode in the other seven. Five patients were intubated at entry, and three patients were intubated during or after efloornithine was started.

Efficacy

In 15 of 33 patient-episodes the patients were
Table 1—Patient-Episode Characteristics and Comparison of Responders and Failures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Episodes (n = 33)</th>
<th>Responders (n = 15)</th>
<th>Failures (n = 16)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females:males</td>
<td>1:32</td>
<td>0:15</td>
<td>1:16</td>
<td>...</td>
</tr>
<tr>
<td>Age, yr</td>
<td>35.7 ± 8.4</td>
<td>36.6 ± 7.1</td>
<td>35.1 ± 9.7</td>
<td>0.6354</td>
</tr>
<tr>
<td>Weight relative to usual weight, %</td>
<td>88.3 ± 9.0</td>
<td>92.9 ± 5.0</td>
<td>83.5 ± 10.1</td>
<td>0.0012</td>
</tr>
<tr>
<td>Weight loss, kg</td>
<td>11.7 ± 9.0</td>
<td>5.3 ± 3.9</td>
<td>12.6 ± 10.1</td>
<td>0.0099</td>
</tr>
<tr>
<td>Prior conventional therapy, d</td>
<td>10.4 ± 4.9</td>
<td>12.2 ± 4.2</td>
<td>8.4 ± 4.7</td>
<td>0.0266</td>
</tr>
<tr>
<td>Prior PTM therapy, d</td>
<td>6.6 ± 3.9</td>
<td>8.3 ± 3.8</td>
<td>4.9 ± 3.6</td>
<td>0.0154</td>
</tr>
<tr>
<td>Prior TS therapy, d</td>
<td>3.8 ± 3.7</td>
<td>3.9 ± 3.9</td>
<td>3.5 ± 3.0</td>
<td>0.8717</td>
</tr>
<tr>
<td>Entry P(a/A)O2 ratio</td>
<td>0.54 ± 0.20</td>
<td>0.64 ± 0.11</td>
<td>0.43 ± 0.21</td>
<td>0.0083</td>
</tr>
<tr>
<td>First episode of PCP</td>
<td>26/33</td>
<td>12/15</td>
<td>13/16</td>
<td>1.0000</td>
</tr>
<tr>
<td>Intubated before eflornithine</td>
<td>6/33</td>
<td>0/15</td>
<td>6/16</td>
<td>0.0177</td>
</tr>
<tr>
<td>Intubated during/after eflornithine</td>
<td>3/33</td>
<td>0/15</td>
<td>3/16</td>
<td>0.2260</td>
</tr>
<tr>
<td>Initial treatment with TS</td>
<td>20/33</td>
<td>10/15</td>
<td>9/16</td>
<td>...</td>
</tr>
<tr>
<td>Initial treatment with PTM</td>
<td>11/33</td>
<td>5/15</td>
<td>5/16</td>
<td>...</td>
</tr>
<tr>
<td>Initial treatment with eflornithine</td>
<td>2/33</td>
<td>0/15</td>
<td>2/16</td>
<td>...</td>
</tr>
</tbody>
</table>

*Comparison of patient-episode characteristics by response (p<0.05 was considered significant).

classified as responders, and in 16, they were classified as failures; and in two, they were not evaluated for efficacy. Two patients were included as responders for their initial episode and as failures for recurrences when eflornithine was administered as initial therapy. Efficacy was not evaluated for two other patients because, although they left the hospital without supplemental oxygen, they completed less than ten (one and six) days of eflornithine treatment. These two patients requested termination of treatment for personal reasons against medical advice and were lost to follow-up. Neither experienced any adverse effects attributable to eflornithine, and neither required oxygen supplementation for outpatient use.

Previous Therapy

Therapy for PCP prior to initiation of eflornithine and the reasons for discontinuation are summarized in Table 2. In 20 of 33 episodes, patients had received treatment with both conventional agents. Of the 20 patients, 16 had not improved during sequential treatment with TS and PTM, four had developed adverse reactions to TS and PTM, and three had suffered an adverse reaction to TS and had shown no improvement with PTM.

In the other 13 episodes, two patients had been treated with TS alone, nine patients had been treated with PTM alone, and two patients had received eflornithine as initial therapy because they had responded to eflornithine treatment for a previous episode of PCP.

Treatment Responses

Of the 15 responders, 2 received eflornithine because of intolerance of conventional therapy, and 13 were treated after showing no response to 10 or more days of therapy with TS or PTM. Four of 15 responders were alive and without recurrence of PCP at the time of last follow-up after surviving 503 ± 105 days (range, 444 to 661 days). Five of 15 responders moved out of

Table 2—Summary of Outcome of Prior Conventional Therapy*

<table>
<thead>
<tr>
<th>Classification</th>
<th>Responders (n = 15)</th>
<th>Failures (n = 16)</th>
<th>Un evaluable (n = 2)</th>
<th>Total (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By type of prior therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with TS only</td>
<td>0/15 (0)</td>
<td>2/16 (12)</td>
<td>0/2 (0)</td>
<td>2/33 (6)</td>
</tr>
<tr>
<td>Treated with PTM only</td>
<td>5/15 (33)</td>
<td>3/16 (19)</td>
<td>1/2 (50)</td>
<td>9/33 (27)</td>
</tr>
<tr>
<td>Treated with TS and PTM</td>
<td>10/15 (67)</td>
<td>9/16 (56)</td>
<td>1/2 (50)</td>
<td>20/33 (61)</td>
</tr>
<tr>
<td>No TS or PTM</td>
<td>0/15 (0)</td>
<td>2/16 (12)</td>
<td>0/2 (0)</td>
<td>2/33 (6)</td>
</tr>
<tr>
<td>By intolerance of prior therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerant of TS</td>
<td>5/10 (50)</td>
<td>3/11 (27)</td>
<td>1/1 (100)</td>
<td>9/22 (41)</td>
</tr>
<tr>
<td>Intolerant of PTM</td>
<td>6/15 (40)</td>
<td>0/12 (0)</td>
<td>0/2 (0)</td>
<td>6/29 (21)</td>
</tr>
<tr>
<td>Intolerant of TS and PTM</td>
<td>4/10 (40)</td>
<td>0/9 (0)</td>
<td>0/1 (0)</td>
<td>4/20 (20)</td>
</tr>
<tr>
<td>By response to prior therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No response to TS</td>
<td>8/10 (80)</td>
<td>9/11 (82)</td>
<td>1/1 (100)</td>
<td>18/22 (82)</td>
</tr>
<tr>
<td>No response to PTM</td>
<td>13/15 (87)</td>
<td>12/12 (100)</td>
<td>2/5 (100)</td>
<td>27/29 (93)</td>
</tr>
<tr>
<td>No response to TS and PTM</td>
<td>8/10 (80)</td>
<td>7/9 (78)</td>
<td>1/1 (100)</td>
<td>16/20 (80)</td>
</tr>
</tbody>
</table>

*Denominator in each fraction is the number of patient-episodes in each category in which the indicated treatment was used. Values in parentheses are percentages.
state and were lost to follow-up after surviving 19 to 205 days. Four of 15 responders died of a non-PCP-related cause: two deaths were attributed to AIDS-related central nervous system disease after 36 and 238 days of survival, and two deaths were attributed to pulmonary and lymphatic Kaposi's sarcoma without evidence of PCP after 58 and 81 days of survival.

**Treatment Failures**

Twelve of the 16 patients who were classified as treatment failures died within 1 to 9 days of initiation of eflornithine treatment. Severe thrombocytopenia developed in two cases, and therapy was terminated. One patient responded to parenteral therapy, but a recurrence developed while the patient was receiving oral therapy as an outpatient. One patient was discharged with supplemental oxygen and died at home after refusing readmission for progressive respiratory insufficiency. The two patients who received eflornithine as initial therapy for a recurrence of PCP are described in detail.

In the first recurrence, PCP developed 103 days after completion of the first course of eflornithine. Following 12 days of intravenous eflornithine, bleeding accompanied by a nadir platelet count of 7,000/cu mm was observed, and TS was substituted for eflornithine treatment. After 12 days of TS treatment, the patient was placed on mechanical ventilation but died nine days later of respiratory failure due to Enterobacter pneumonia complicated by pulmonary Kaposi's sarcoma. No Pneumocystis cysts were found in lung tissue at autopsy.

In the second recurrence, PCP developed 267 days after completion of the first course of eflornithine. The patient received 14 days of intravenous eflornithine and was discharged on a regimen of oral eflornithine. Respiratory status deteriorated after discharge, and the patient was readmitted ten days later. Repeat bronchoscopy was positive for *P. carinii* cysts. Mechanical ventilation was started after six days of hospitalization, and intravenous PTM was substituted for eflornithine. The patient died six days later of respiratory failure complicated by pulmonary tuberculosis.

**Patient Characteristics by Outcome**

Patient characteristics of responders and failures are summarized and compared in Table 1. No statistically significant difference between responder and failure episodes was found for age, number of days of prior TS therapy, whether the PCP episode was the first or not, and whether the patient was intubated after entry.

Responders and failures differed by weight at entry as a percentage of their preillness weight (*p* = 0.0012), reported weight loss (*p* = 0.0039), total number of days of previous conventional therapy (*p* = 0.0266), number of days of previous PTM therapy (*p* = 0.0154), initial

<table>
<thead>
<tr>
<th>Infection or Diseases</th>
<th>Responders (n = 15)</th>
<th>Failures (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Kaposi's lesions</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary CMV (BAL)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Disseminated CMV (autopsy)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total occurrences</td>
<td>1 (1)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

*Values are numbers of occurrences; values in parentheses are numbers of patients. CMV = cytomegalovirus infection; BAL = bronchoalveolar lavage.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21638/)

**Figure 1.** Pattern of depletion and recovery of thrombocytes in five patients who developed severe thrombocytopenia (platelet count below 20,000/cu mm) during eflornithine treatment (IV = intravenous; PO = oral). In four patients, intravenous therapy was halted in the hospital because of a rapid decline in platelet count; platelet counts recovered in four days in one and in five to seven days in the other three. Oral therapy was started following recovery in one of the four, and platelet counts again declined but remained above 150,000/cu mm. In one patient, eflornithine was terminated because severe thrombocytopenia occurred during oral therapy as an outpatient. In this patient, platelet counts normalized between 8 and 11 days later.

<table>
<thead>
<tr>
<th>Patients with severe thrombocytopenia (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21638/" alt="Thrombocytopenia Graph" /></td>
</tr>
</tbody>
</table>
P(a/A)O₂ (p = 0.0083), and whether mechanical ventilation was instituted prior to initiation of eflo

Concurrent Infections

Concurrent infections and pulmonary diseases are summarized in Table 3. There was one occurrence of Staphylococcus epidermidis bacteremia among the responders and one case of Escherichia coli bacteremia among the failures. Episodes resulting in treatment failure were much more likely to be characterized by concurrent systemic or pulmonary infections and pulmonary Kaposi lesions compared to responder episodes.

Hematologic Adverse Effects

The most significant hematologic adverse effect was thrombocytopenia, which occurred in 12 of 19 patients (63 percent) who received eflo therapy for ten or more days. No patient treated for less than ten days met the definition of thrombocytopenia. In these 12 patients, the platelet count did not begin to decline until after day 7. Platelet counts often fell precipitously at about day 10 and continued to fall for several days after discontinuation of the drug. The nadir platelet count in the patients in whom thrombocytopenia developed averaged 33,500 ± 31,500/cu mm (median, 19,500/cu mm). The average time required for the platelet count to recover to at least 150,000/cu mm was 10.8 ± 6.6 days after discontinuation of eflo
dine. Figure 1 illustrates the pattern of decline of the platelet count in five patients in whom the platelet count decreased to less than 20,000/cu mm. Leukopenia occurred in 14 of 33 episodes, and anemia occurred in 9 of 33 episodes.

One patient had an upper gastrointestinal tract hemorrhage, and a second patient had an intracerebral hemorrhage associated with eflo-induced thrombocytopenia. These patients had platelet counts of less than 10,000/cu mm at the time of bleeding.

Loss of Hearing

Three patients developed symptoms of hearing loss after eflo therapy. One patient who had no subjective hearing difficulty requested a posttreatment audiogram; it was normal. Two patients complained of hearing problems while receiving oral eflo; they were found to have abnormal audiograms, and eflo was discontinued. Subsequent audiograms showed partial reversal of the hearing deficit in these two patients. One patient complained of deafness one year after eflo treatment upon admission for another episode of PCP. Audiometric studies were abnormal at that time, but follow-up could not be done because the patient died several days after admission.

Other Adverse Effects

Adverse experiences are summarized in Table 4. The most frequent nonhematologic adverse effects were anorexia in 12 of 33, nausea in 11 of 33, and onset or exacerbation of diarrhea in 10 of 33 episodes.

Efficacy

Treatment of PCP with either TS or PTM has resulted in response rates of 60 to 80 percent. The frequency of serious, treatment-limiting adverse reactions is very high for both agents. Therefore, alternative drug agents for treating PCP in patients

Table 4—Summary of Adverse Effects Associated with Eflo

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Responders (n = 15)</th>
<th>Failures (n = 16)</th>
<th>Unevaluable (n = 2)</th>
<th>Total (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>6 (40.0)</td>
<td>5 (31.3)</td>
<td>1 (50.0)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Diarrhea†</td>
<td>5 (33.3)</td>
<td>4 (25.0)</td>
<td>1 (50.0)</td>
<td>10 (30.3)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (20.0)</td>
<td>2 (12.5)</td>
<td>0 (0.0)</td>
<td>5 (15.2)</td>
</tr>
<tr>
<td>Hepatitis†</td>
<td>0 (0.0)</td>
<td>1 (6.3)</td>
<td>0 (0.0)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>7 (46.7)</td>
<td>3 (18.8)</td>
<td>1 (50.0)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Anemia§</td>
<td>6 (40.0)</td>
<td>3 (18.8)</td>
<td>0 (0.0)</td>
<td>9 (27.3)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (13.3)</td>
<td>2 (12.5)</td>
<td>0 (0.0)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Leukopenia‖</td>
<td>9 (60.0)</td>
<td>4 (25.0)</td>
<td>1 (50.0)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Thrombocytopenia†</td>
<td>9 (60.0)</td>
<td>4 (25.0)</td>
<td>0 (0.0)</td>
<td>13 (39.4)</td>
</tr>
<tr>
<td>Loss of hearing#</td>
<td>2 (13.3)</td>
<td>1 (6.3)</td>
<td>0 (0.0)</td>
<td>3 (9.1)</td>
</tr>
</tbody>
</table>

*Values are numbers of patient-episodes, with percentages in parentheses.
†Onset or increase of diarrhea, with three or more loose stools a day.
‡An increase in serum transaminase levels to more than five times the upper limit of normal.
§Nadir hematocrit was less than 90 percent of baseline value.
||Nadir leukocyte count was less than 50 percent of baseline value.
‖Nadir platelet count was less than 100,000 (all patients had entry platelet counts of 150,000 or more).
#Hearing loss defined as follows: (1) comparison of pre- and post-treatment audiograms showed a ≥20-dB increase in hearing threshold at one or more tested frequencies; or (2) patients without pretreatment audiometry complained of hearing loss and had an audiogram showing at least a 20-dB increase above the normal threshold at one or more frequencies after treatment was completed.

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with AIDS are needed.

There is an inherent problem in evaluating efficacy in a compassionate-treatment trial. Patients receive compassionate treatment because, in the judgment of their physicians, they are at risk of significant morbidity or mortality if conventional treatment is continued. There is, of course, no way to determine the probability of a mortal event or the probable cost of a morbid event with continued conventional treatment.

In this series of patients with AIDS who were intolerant of and/or unresponsive to conventional therapy for PCP, eflornithine was associated with a clinical response in 15 of 33 episodes of PCP by intention to treat. Of the 15 responders, two were improving with previous conventional therapy. Thirteen responders were not improving after five or more days of treatment with one or both conventional agents. Ten of 15 responders had received ten or more days of treatment with sequential PTM and TS without responding. This suggests that eflornithine is an effective treatment.

It is not certain that all eflornithine responders would ultimately have been classified as failures if conventional therapy had been continued. Certain patient characteristics at entry were strongly associated with likelihood of response to eflornithine (Table 1). Entry PaO2 (p = 0.0083), length of prior conventional therapy (p = 0.0266), length of prior treatment with PTM (p = 0.0154), and weight as a percentage of usual preillness weight (p = 0.0012) were positively associated with likelihood of response. A negative association was found for weight loss (p = 0.0039) and the need for mechanical ventilation at entry (p = 0.0177).

As already noted, patients classified as eflornithine responders received more days of prior conventional therapy than failures. There was no evidence of any difference in the amount of TS received, but there was a difference in the amount of PTM received by these two groups. This difference in prior PTM therapy may have been caused by prescriber bias in favor of continuing PTM rather than TS in the face of a suboptimal response. In this series, TS was offered first in 20 of 33 eflornithine patient-episodes, compared with 11 of 33 for PTM. Pentamidine was more likely to be administered as alternative conventional therapy for patients intolerant of or not rapidly responsive to TS. It is probable that this resulted in longer treatment with PTM in the absence of a third conventional drug. An alternative explanation is that PTM, which binds avidly to various body tissues including lung tissue, may have acted in conjunction with eflornithine to increase the probability of a response.

The entry PaO2 ratio ranged from 0.076 to 0.237 in the five patients who required mechanical ventilation at entry. Four of the five died within four days of entry, and the fifth patient survived for 13 days. It is difficult to evaluate efficacy in such patients because they may die of irreversible complications of respiratory failure rather than PCP. None of these patients received concomitant therapy with adrenal corticosteroids, since the benefit of this maneuver was not known at the time of this compassionate trial.16,17

Adverse Effects

The most significant toxicity associated with eflornithine was thrombocytopenia, which was often accompanied by progressive decline in peripheral erythrocyte and leukocyte counts. This may be the result of a cumulative suppressive effect on the bone marrow. Thirteen of 33 patient-episodes (39 percent) resulted in thrombocytopenia, and there was a strong association with length of treatment. This probably underestimates the true risk of thrombocytopenia, since thrombocytopenia was observed in 12 of 19 patient-episodes (63 percent) involving treatment for ten or more days. Platelet counts returned to normal within four to seven days after discontinuation of the drug. Recognition of this fact prompted a change in the entry and stopping criteria from ≥100,000 to ≥150,000 platelets/µl and from ≥75,000 to ≥100,000 platelets/µl, respectively, during the course of the study.

Loss of Hearing

It is reasonable to conclude that auditory damage is a potential adverse effect of treatment with eflornithine, but it is not possible to assess its prevalence from these data. No attempt was made to determine the incidence of subclinical loss of hearing associated with eflornithine treatment.

Pharmacokinetics

Limited information is available concerning the disposition of eflornithine in humans. In a study of six volunteers,18 an apparent volume of distribution of 0.34 L/kg and an elimination half-life of 199 min were reported, using a one-compartment model. The fraction of unchanged drug excreted in the urine was 83 percent following intravenous administration. It is highly probable that the drug will accumulate in patients with renal insufficiency and increase the risk of adverse effects. In this series, we were unable to correlate renal insufficiency with frequency or severity of adverse effects.

Therapy in Unresponsive or Intolerant Patients

In unresponsive or intolerant patients with PCP, therapy may be continued with a reduced dose of the toxicity-inducing agent.19,20 In the case of TS, dosage reduction may reduce the risk of neutropenia, but
other adverse effects, such as intolerable rash, severe hepatitis, and severe nausea and vomiting, may necessitate drug discontinuance. Decreased dosage of parenteral PTM has been suggested for patients who develop hypoglycemia or renal insufficiency, although a relationship between dosage and these adverse effects has not been clearly established.

Alternative, unconventional agents include combinations of a dihydrofolate reductase inhibitor and a sulfone, such as trimethoprim-dapsone, pyrimethamine-sulfadiazine, or pyrimethamine-sulfadoxine. However, these treatments are associated with significant risk of adverse effects. Cross-reactions between sulfu compounds are particularly common.

Trimetrexate-leucovorin combination is an investigational treatment for PCP. Trimetrexate is a dihydrofolate reductase inhibitor with 1,500 times the in vitro activity of trimethoprim. It must be administered in combination with leucovorin to spare mammalian cells from toxicity. It is associated with a 90 percent response rate but carries a significant risk of severe bone marrow suppression in the absence of intent monitoring. Six of ten responders relapsed within three months in one series. Treatment is costly because of the need for concurrent leucovorin.

Trials of aerosolized PTM for treating mild to moderate episodes of acute PCP have shown promising results. A potential disadvantage of this treatment modality is inadequate alveolar delivery of drug in patients with extensive alveolar involvement. Two randomized trials comparing aerosolized PTM with intravenous PTM demonstrated similar efficacy in mild PCP episodes, but the aerosolized route was less efficacious in severe episodes.

**Conclusions**

The role of efornithine as an alternative treatment for PCP is not fully defined, but it appears promising as an alternative therapy for PCP unresponsive to other agents. Clinical remission of PCP was achieved in 15 of 33 patient-episodes, including 13 in patients who had been previously unresponsive to or intolerant of conventional therapy. Risk of bone marrow suppression mandates that peripheral erythocyte, leucocyte, and especially thrombocyte counts must be carefully monitored. Occurrence of thrombocytopenia may delay or prevent completion of the treatment regimen used in this series. Concurrent infections and respiratory insufficiency are associated with a poor response to efornithine therapy.

Comparative clinical trials of efornithine as initial therapy are still needed to define more fully its role in the treatment of PCP. Future studies should also address the issue of optimal dosage and duration of treatment, as well as dosage guidelines for patients with renal insufficiency.

**References**

20. Conte JE, Holland H, Golden JA. Inhaled or reduced-dose PTM.


