Aerosolized Pentamidine as Second Line Therapy in Patients with AIDS and Pneumocystis carinii Pneumonia*

A. Bruce Montgomery, M.D.; Robert J. Debs, M.D.; John M. Luce, M.D., F.C.C.P.; Kevin J. Corkery, R. R. T.; Joan Turner, R.N.; and Philip C. Hopewell, M.D.

The use of aerosolized pentamidine was investigated in ten patients with the acquired immunodeficiency syndrome (AIDS) and Pneumocystis carinii pneumonia (PCP) who had previous or concurrent severe adverse reactions or contraindications to trimethoprim-sulfamethoxazole or parenteral pentamidine. A dose of 600 mg pentamidine in 6 ml sterile water, aerosolized in a small-particle producing jet nebulizer was administered for 25 minutes once daily for an average of 10.5 days to these ten patients. All patients improved their arterial O\textsubscript{2} saturation and showed clinical and roentgenographic improvement within six to 21 days of aerosol pentamidine therapy. No adverse systemic reactions occurred. The results of this small open trial indicate that aerosolized pentamidine is effective and can be given safely to AIDS patients with PCP who have had adverse reactions to trimethoprim-sulfamethoxazole or parenteral pentamidine.

(Chest 1989; 95:747-50)

\begin{equation*}
\text{TMP/SMX} = \text{Trimethoprim-sulfamethoxazole}
\end{equation*}

S
tandard therapy for Pneumocystis carinii pneumonia (PCP) presently consists of either oral and intravenous trimethoprim-sulfamethoxazole (TMP/SMX) or intravenous or intramuscular pentamidine isethionate.\textsuperscript{1,2} Although these agents are equally effective in first episodes of PCP in patients with AIDS, both cause side effects sufficiently severe to require a change of therapy in at least 40 percent of patients. In addition, a substantial number of patients become intolerant to both agents.\textsuperscript{1,4}

Recently, administration of pentamidine in the form of an inhaled aerosol has been shown to be effective for first episodes of PCP in patients with AIDS.\textsuperscript{5,6} Few adverse systemic reactions occurred in these patients, presumably because serum concentrations of pentamidine were low.\textsuperscript{5,6} Because of the efficacy of aerosolized pentamidine in these pilot studies, we began to use this form of therapy on a compassionate basis in AIDS patients with PCP for whom standard therapy presented a significant hazard. This report summarizes our experience with aerosolized pentamidine in this selected group of patients.

METHODS

Beginning in March 1987, patients with AIDS and PCP were considered as candidates for aerosolized pentamidine if they either had adverse reactions to TMP/SMX or parenteral pentamidine or if they failed to respond to these agents. The specific characteristics of these patients are listed in Table 1.

*From the Medical Service, Respiratory Care Service, San Francisco General Hospital Medical Center, Cancer Research Institute, and Department of Medicine, University of California, San Francisco. This work was supported by funds provided by the State of California and allocated on the recommendation of the Universitywide Task Force on AIDS.

Manuscript received July 5; revision accepted August 8.

The diagnosis of PCP in these patients was based on finding the organism in induced sputum or bronchoalveolar lavage specimens. The definitions of significant adverse reactions to TMP/SMX and pentamidine were based on criteria used in a previously reported prospective comparison of these agents at our institution (Table 2).\textsuperscript{3}

As described previously, treatment consisted of inhalation of an aerosol of pentamidine isethionate once a day. The dose was 600 mg dissolved in 6 ml of sterile water and placed in a baffled jet nebulizer with a scavenger filter for expired pentamidine (Respigard II, Marquest, Englewood, CO). The particle size in this system was 1.42 ± 1.88 mass median aerodynamic diameter and geometric standard deviation.\textsuperscript{9} Each inhalation session lasted approximately 25 minutes. Patients who coughed during treatment were pretreated with aerosolized metaproterenol prior to subsequent therapy. Aerosolized pentamidine was continued until hypoxemia, dyspnea, and fever had resolved or substantially improved, in which case, the therapy was discontinued at the option of the attending physicians.

All patients were examined daily. Laboratory studies including complete blood count, platelet count, serum electrolytes, glucose, creatinine, and tests of liver function were done at time inhaled therapy was begun and at least every three days thereafter. Chest x-ray films and arterial blood gas tensions (PaO\textsubscript{2}) or oxygen saturations on ambient air were obtained at initiation of aerosol therapy and as clinically indicated thereafter. Failure of aerosolized pentamidine therapy was defined as the following: (1) worsening of respiratory symptoms, and deterioration of chest x-ray films and arterial PaO\textsubscript{2} or pulse oximetry while on therapy; (2) development of severe adverse reactions as defined in Table 2; and (3) worsening of a preexisting severe adverse reaction.

RESULTS

Of 272 patients with AIDS and PCP diagnosed at San Francisco General Hospital between March 1, 1987, and January 11, 1988, ten met the eligibility criteria. All consented to be treated with aerosol pentamidine on a compassionate basis. The mean duration of aerosol treatment was 10.5 days (range five to 17) and the mean total duration of combined...
standard and aerosol treatment was 20.8 days. All patients had substantial improvement as manifested by a \( \text{PaO}_2 \) greater than 70 mm Hg or an arterial saturation greater than 94 percent on room air, normalization of temperature, and improving chest roentgenograms. All patients survived to the end of treatment.

During aerosolized pentamidine therapy, six of ten patients had cough requiring pretreatment with aerosolized metaproterenol by metered dose inhaler. The cough tended to resolve during subsequent therapy. Clinically detectable bronchospasm did not occur in any of the ten patients. No other adverse reactions occurred. In addition, all previous adverse reactions attributed to prior therapy resolved.

**DISCUSSION**

This report suggests that aerosolized pentamidine is an effective and nontoxic therapy for PCP in AIDS patients who have previous or concurrent severe adverse reactions to parenteral pentamidine and/or TMP/SMX. None of the ten patients in this study had additional severe adverse reactions, and all were treated successfully. The absence of treatment failures in this small group was not surprising; these patients were not deteriorating clinically, and patients such as these who require a change of therapy because of toxicity have been shown to have a subsequent failure rate of only 11 percent. Nevertheless, the lack of toxicity to aerosolized pentamidine was heartening.

Several potential options exist for patients who are intolerant of both TMP/SMX and parenteral pentamidine and require further therapy. Some patients may be rechallenged with TMP/SMX, particularly when it is not clear that TMP/SMX was responsible for previous problems. Another approach is to continue therapy with a reduced dose of the offending agent. This may lead to a decrease in adverse reactions such as leukopenia, but it probably would be inadvisable in patients with reactions such as severe rash and mucositis.

Treatment with other dihydrofololate reductase inhibitors and sulfa or sulfone combinations such as pyrimethamine/sulfadiazine or trimethoprim/dapsone is another option in patients with intolerance to both TMP/SMX and parenteral pentamidine. However, cross reactivity among sulfa compounds is common and may be especially common among AIDS patients. Thus, although the combination of oral trimethoprim/dapsone has been found to have a 13 to 25 percent incidence of severe adverse reactions compared to 50 percent with TMP/SMX, significant toxicity with this agent still occurs.

Other experimental antipneumocystis agents in-
Table 2—Definitions of Major and Minor Adverse Reactions*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>≤750 Neutrophils/μL 750 Neutrophils/μL to 50% neutrophils below baseline</td>
<td>4000 to 50% below baseline</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>≤40,000/μL</td>
<td>40,000 to 50% below baseline</td>
</tr>
<tr>
<td>Rise in creatinine</td>
<td>≥3.0 mg/dL</td>
<td>.5 Above baseline to 3.0</td>
</tr>
<tr>
<td>Liver function abnormalities</td>
<td>SGOT or SGPT ≥5x normal</td>
<td>2x-5x normal</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>&lt;50 mg/dL</td>
<td>&lt;75 mg/dL</td>
</tr>
<tr>
<td>Rash</td>
<td>With fever or mucositis</td>
<td>Without fever or mucositis</td>
</tr>
<tr>
<td>Cough</td>
<td>Cough or broncho-spasm uncontrolled by metaproterenol preventing &gt;50% of delivered dose for greater than 2 days</td>
<td>Cough</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Intractable</td>
<td>Controlled with antiemetics</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Systolic BP&lt;90</td>
<td>Systolic BP&lt;90 transiently</td>
</tr>
<tr>
<td>Decreased mental status</td>
<td>New disorientation to two of the following: name, place, time</td>
<td>New disorientation to one of either name, place, or person</td>
</tr>
</tbody>
</table>

*Modified from Montgomery et al.5,7

Include trimetrexate and difluoromethylornithine.4,13 Trimetrexate has been used with good results in patients with prior drug reactions to sulfa compounds.4 Difluoromethylornithine has been used in numerous patients as salvage therapy, but its efficacy as sole therapy has not been investigated.13

Lower dose parenteral pentamidine (3 mg/kg/day) has been advocated as a way to decrease pentamidine toxicity.6 This approach is justified if pentamidine toxicity, especially hypoglycemia, is dependent on the cumulative dose. However, dose dependency in this situation is not well established. Furthermore, the safety of this approach in the presence of toxicity has not been tested.

Aerosolized pentamidine is associated with low systemic pentamidine concentrations but high lung levels. Because P carinii organisms are limited nearly exclusively to the alveolar spaces, high alveolar concentrations of the drug should be effective even with low systemic absorption.5,7,14,15 Two human treatment trials with aerosolized pentamidine have been reported.5,6 In the first, which used the identical treatment regimen reported in this study, 13 of 15 patients responded and none had major adverse reactions. In the other study, nine of 13 patients responded. Two patients developed leukopenia, but both were also receiving zidovudine (AZT).

The major theoretic disadvantages of aerosolized pentamidine are possible limited alveolar deposition in patients with extensive alveolar filling and airway toxicity. However, high alveolar levels have been confirmed by bronchoalveolar lavage 16 to 24 hours after aerosol delivery in patients with mild to moderate lung disease.7 The patients in this study all had moderate or mild PCP at the time aerosol therapy was initiated and were not deteriorating in their respiratory status. Unfortunately, aerosolized pentamidine therapy has not been tested in patients with worsening infiltrates or respiratory failure.

Cough is common among AIDS patients receiving aerosolized pentamidine therapy. This is perhaps due to the fact that pentamidine isethionate is a sulfonate, and the concentrations used are tenfold to 100-fold higher than those used in SO, challenge studies of asthmatics.16 The aerosol particle size of 1.42μ, with less than 5 percent of particles greater than 4μ, minimizes airway deposition and should minimize airway irritation, as demonstrated in the patients in this study.9 If a larger particle size were used, less alveolar and more airway deposition would occur; this in turn might cause more airway irritation and less therapeutic efficacy.17

In conclusion, aerosolized pentamidine seems to be efficacious and nontoxic as continuation therapy in patients with mild to moderate PCP who have experienced significant reactions to standard therapy. Furthermore, this therapy has been previously shown to not require hospitalization and may not require extensive monitoring for adverse reactions. Further studies of aerosol pentamidine are needed to define its role both as a primary and second line agent.

REFERENCES

Occupational Health and Safety Institute

The Fourth Annual OHSI will be held at Tufts University, Medford, Massachusetts, June 13-17. Cosponsors are the Occupational Health Program, University of Massachusetts Medical School and Harvard Educational Resource Center, Harvard University School of Public Health. For information, contact the Occupational Health Program, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester 01655 (508:856-2322).