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AEROSOLISED PENTAMIDINE FOR PNEUMOCYSTIS CARINII PNEUMONIA IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME

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SUMMARY

The goal of this study was to evaluate inhaled pentamidine for the treatment of patients with mild and moderate **Pneumocystis carinii** pneumonitis. Eight adults with AIDS and pneumocystis pneumonia (4 with a first episode and 4 with a repeat pneumocystosis) received daily inhalations of aerosol pentamidine isethionate for 21 days. Six patients were treated with doses of 300 mg of pentamidine and the remaining 2 received 600 mg every day. In the 300 mg treatment group, 2 individuals showed discrete and transient neutropenia. However, both subjects that received 600 mg of aerosol pentamidine daily developed leukopenia. One of them had major toxicity (overall severe intolerance of 12.5%) that required drug discontinuation and did not allow any analysis of the treatment efficacy. Of the 7 evaluable patients, 6 (88%) completed the treatment successfuly. One subject of the 300 mg regimen experienced an early recurrence. In conclusion, inhaled pentamidine is an effective treatment for mild and moderate cases of **P. carinii** pneumonia. It is less toxic than standard anti-pneumocystis therapy and is suitable for outpatient use.

KEY WORDS: Acquired immunodeficiency syndrome; **Pneumocystis carinii** pneumonia; Pentamidine; Inhalatory therapy.

INTRODUCTION

A remarkable clinical feature of the acquired immunodeficiency syndrome (AIDS) has been the extremely high incidence of **Pneumocystis carinii** pneumonia (PCP). In North America, pneumocystosis is the initial AIDS-defining process in 65% of patients infected with human immunodeficiency virus (HIV) and at least 80% of individuals with AIDS ultimately develop one or more episodes of **P. carinii** pneumonitis[22, 23]. There is a dearth of information on infectious complications of AIDS in third world countries. Nevertheless, the few studies previously done in Brazil indicate that PCP is very frequent in our country too. **P. carinii** was identified in 62% of HIV infected subjects with respiratory complaints[32] and overall was reported in 43% of AIDS

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patients[4], although it was found only in 13% of autopsy cases[19].

The standard therapy for **P. carinii** pneumonia consists of either trimethoprim-sulfamethoxazole given intravenously or orally or pentamidine isethionate administered intravenously or intramuscularly. In patients with AIDS these drugs are associated with a 50% incidence of significant toxicity and a failure rate of approximately 25%[9, 12, 16, 20, 28, 33]. Because of the expansion of the AIDS epidemic, novel treatment regimens have been searched. Among the new drugs, dapsone with trimethoprim, eflornithine, clindamycin with primaquine and trimetrexate have shown the most promising results[1, 15, 17, 29, 30].

Another alternative has been the administration of pentamidine isethionate by inhalatory route[5, 21, 31]. Due to the intra-alveolar location of **P. carinii**, aerosolisation of pentamidine should provide an effective, site-specific and hence less systemically toxic method of therapy and prophylaxis. We report a trial that demonstrates the safety and therapeutic activity of pentamidine isethionate inhalations for mild to moderate **P. carinii** pneumonia in patients with AIDS.

PATIENTS AND METHODS

Between August, 1988 and January, 1989, all the patients with the acquired immunodeficiency syndrome and **P. carinii** pneumonia, who were seen at the Division of Infectious Diseases of the Hospital das Clinicas of the University of São Paulo School of Medicine, were considered for inclusion in the trial. Of the 15 individuals 18 years or older who were screened, 8 subjects were admitted to this study. Patients were excluded for the following reasons: 1) arterial blood oxygen less than 55 mmHg on room air; 2) empirical therapy for more than 48 hours; 3) unstable clinical conditions or predicted survival of less than 2 weeks because of other complications of AIDS; 4) concomitant administration of pyrimethamine-sulfonamide combination; 5) history of asthma. The study protocol was part of a multicenter trial organized by Rhône-Poulenc and it was approved by the Research Committee of the Department of Infectious Diseases of the Hospital das Clinicas of the University of São Paulo School of Medicine. Informed consent was obtained from all the patients.

The diagnosis of PCP was based on finding the organism either in induced sputum[2, 26] or bronchoalveolar lavage[3, 14] stained with toluidine blue O, or on histologic evaluation of transbronchial biopsies. All sputum and lavage specimens were also examined with Gram's stain, Ziehl Neelsen technique, potassium hydroxide and cultured for mycobateria, fungi and viruses.

The treatment consisted of inhalation of 300 or 600 mg of pentamidine isethionate aerosol (Rhodia, São Paulo, SP) once daily for 21 days. The pentamidine was dissolved in 5 ml of sterile water and administered with a Respigard nebuliser (Marquest, Englewood, Colorado). Each inhalation session lasted approximately 20 min. Patients were premedicated with salbutamol 30 min before pentamidine administration.

All the subjects had initially a complete history and physical examination, followed by daily observations. Chest radiographs and laboratory studies, which consisted of arterial blood gases, complete blood counts, liver function tests, fasten glucose and serum creatinine, were performed at study admission and repeated every 4 days until completion of the protocol. Failure to respond to the treatment was defined as worsening of symptoms after at least 4 days of inhalatory pentamidine or lack of improvement after 7 days of therapy. Patients who did not respond to the inhalatory therapy were given intravenous trimethoprim-sulfamethoxazole. The subjects who improved on aerosolised pentamidine treatment, as suggested by clinical status and blood gas analysis, were observed for an additional month in order to detect early recurrences.

RESULTS

Eight adult AIDS patients with ***P. carinii*** were included in the study. As shown in Table 1, there were 6 males and 2 females, 6 white and 2 black subjects, with a mean age of 33.25 years (range of 24 to 52). The risk factors for HIV infection were the following: 4 individuals reported homosexual activities; 3 were intravenous drug users and 1 had a blood transfusion history. Three subjects presented with their initial AIDS-defining process and the remaining 5 had been

TABLE 1
Demographic characteristics of the study population

Age	33.25 (24 to 52)
	nº of patients
Sex	
males	6 (75%)
females	2 (25%)
Ethnicity	
white	6 (75%)
black	2 (25%)
Risk factors	
homosexuals/bisexuals	4 (50%)
drug users	3 (37%)
blood transfusion	1 (13%)

identified as AIDS patients 3 ± 4.9 months before entry to the trial. All the individuals included in the study showed additional opportunistic diseases (Table 2): 6 had candidiasis, 2 patients suffered from pulmonary tuberculosis, 3 had viral infections, 1 individual had staphylococcal sepsis, 3 had recurrent diarrhea and 2 displayed neurotoxoplasmosis. The diagnosis of **P. carinii** pneumonitis relied on induced sputum exam in 4 patients, bronchoalveolar lavage in 2 and histopathologic evaluation in the remaining 2 subjects.

TABLE 2
Opportunistic infections and neoplasms in 8 AIDS patients

Diagnosis	Cases
Candidiasis, oro-esophageal	6
Tuberculosis	2
Viral infections	3
cytomegalovirus colitis or enteritis	1
genital **Herpes simplex**	1
cutaneous zoster	1
Staphyloccocus aureus sepsis	1
Kaposi sarcoma	3
Diarrhea	4
cytomegalovirus colitis or enteritis	1
Giardia lamblia	1
Isospora belli	1
Strongyloides stercoralis	1
Central nervous system toxoplasmosis	2

The first 6 patients enrolled in the study received daily inhalations with 300 mg of pentamidine and the following 2 individuals with AIDS and pneumocystis pneumonia were treated with 600 mg of pentamidine (Table 3). Overall, 6 subjects successfully completed the therapeutic regimen. One patient failed to improve on aerosolised pentamidine and was switched to intravenous trimethoprim-sulfamethoxazole. However, his respiratory failure worsened even with the alternative treatment and he eventually died. Patient 8 was excluded from the analysis of treatment efficacy because he developed severe adverse reactions while on pentamidine and, although his pulmonary status was improving, the drug was discontinued. Overall, among the 7 evaluable individuals, the efficacy rate was 86%. The patients who responded to the inhalatory pentamidine treatment reported subjective improvement of the respiratory symptoms after 6 ± 3.4 days (Table 4). There was a significant

TABLE 3
Outcome with inhalatory pentamidine for **P. carinii** pneumonia in AIDS patients

Patient	Episode nº	Dose (mg)	Toxicity	Outcome
1	1	300	none	improved
2	1	300	none	improved
3	2	300	leukopenia	improved
4	1	300	none	improved
5	2	300	none	progression
6	2	300	leukopenia	improved
7	1	600	leukopenia	improved
8	2	600	leukopenia, fever, rash, dysglicemia	withdrawal

TABLE 4
Clinical and laboratory course of **P. carinii** pneumonia in 6 AIDS patients who improved with inhalatory pentamidine therapy

Parameter	Time of improvement (days of therapy)
Dyspnea	6 ± 3.4[1]
Respiratory rate < 20	7 ± 2
Arterial blood O_2 > 70 mmHg	5.3 ± 2.3
Temperature < 37.5	2.8 ± 1.6[2]
Chest radiogram	10.6 ± 3.3

1. Numbers indicate mean ± standard deviation.
2. Data were derived from 5 patients without any other cause of fever.

decrease of the respiratory rates and elevation of the arterial blood oxygen above 70 mmHg at 7 ± 2 and 5.3 ± 2.3 days, respectively. Temperatures became normal after 2.8 ± 1.6 days in 5 patients who did not have a concurrent infection that might have determined fever. Two of the 7 subjects who were clinically improving on aerosolised pentamidine showed radiographic deterioration during the first 4 days of treatment and subsequent clearing of the pulmonary infiltrates. Overall, chest radiograms displayed sensible ameloriation after 10.6 ± 3.3 days of therapy and were completely normal at 21 days in 3 of the 4 patients who completed the therapeutic regimen and had no other pulmonary diseases. One of the subjects who improved on 300 mg pentamidine experienced an early recurrence, 14 days after the drug discontinuation. There were no significant differences in clinical or radiographic responses between patients who were presenting the first or second episode of PCP.

Toxic reactions occurred in 4 patients (50%). Of the 6 individuals who received daily doses of 300 mg of inhalatory pentamidine, 2 subjects showed mild and transient leukopenia during the third week of treatment. However, both subjects on 600 mg of pentamidine developed neutropenia during the first week of therapy. Patient 8 had rash, fever, hyperglicemia and his neutrophile counts dropped below $5x10^8$ cells/l. Although the patient's respiratory status was improving, the adverse effects prompted the drug discontinuation. Thus, major toxicity was noted only in the 600 mg dose group. Overall, 12.5% of the AIDS subjects treated with aerosol pentamidine needed to have their therapy changed.

DISCUSSION

This open study shows that aerosolised pentamidine is safe and effective in the treatment of mild to moderate **P. carinii** pneumonia in patients with AIDS. The observed 86% efficacy rate is also in agreement with 2 previous studies of inhalatory pentamidine for pneumocystis pneumonitis in HIV infected individuals. MONTGOMERY et al.[21] and CONTE et al.[5] reported satisfactory responses in 87% of 15 subjects and 90% of 10 patients, respectively. However, GODFREY-FAUSSETT et al.[10] found a 15% efficacy rate after administering aerosol pentamidine tc 13 individuals with AIDS and pneumocystosis. These discrepancies might be explained by the different efficiency of the nebulisers that were used in these studies. As it has already been shown, particle size is a major determinant of location of drug deposition. Furthermore, O'DOHERTY et al.[24], comparing 3 jet nebulisers and an ultrasonic one, concluded that Respigard II and System 22 Mizer (Medicaid) should be used to administer aerosol pentamidine because they conferred the highest pulmonary deposition. Moreover, in the same report, the use of Respigard II, which was employed in the present study too, was associated with the fewest adverse effects.

One of our patients had a recurrence earlier than it might have been expected. This observation is consistent with previous reports[5]. Nevertheless, the numbers are very small and further trials are necessary to establish the risk of early recurrences after aerosol pentamidine for pneumocystosis in AIDS patients.

Our efficacy data are equal to or better than those obtained with trimethoprim-sulfamethoxazole, parenteral pentamidine or trimethoprim-dapsone in mild to moderate **P. carinii** pneumonitis[17, 20, 25, 28, 33]. Although an open study does not allow formal comparisons to be made with other therapies, the criteria for entry to the current trial were similar to those for other protocols. In contrast, trimetrexate, eflornithine and clindamycin-primaquine have been used mostly as salvage therapy[1, 29, 30] in patients who were unresponsive to trimethoprim-sulfamethoxazole and parenteral pentamidine, which precludes any comparison to inhalatory pentamidine.

Aerosol pentamidine was well tolerated. In the group that received 300 mg daily doses, 33% of the patients developed minor transient abnormalities in white blood cell counts. However, both subjects treated with 600 mg of pentamidine showed leukopenia and one of them required withdrawal of the drug. Due to the small numbers, further studies are necessary to establish if this is a significant difference. Overall, major toxicity was observed in 12.5% of the individuals enrolled in the trial. In contrast, standard therapy with trimethoprim-sulfamethoxazole or parenteral pentamidine is associated

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with discontinuation of the initial regimen in up to 55% of patients. Furthermore, trimethoprim-dapsone also demonstrated a 13% to 25% rate of severe toxicity in AIDS subjects[17]. Previous studies showed that daily pentamidine inhalations do not impair pulmonary functions, but may determine bronchial bleeding.

It is interesting to note that many individuals have received aerosolised pentamidine as outpatients. In this study, only 2 subjects could be discharged before inhalatory therapy completion. Some of the other individuals could have gone home earlier except for other AIDS related complications or social problems.

P. carinii pneumonia commonly recurs; a recent study reported relapse rates of 18% at 6 months, 46% at 9 months and 65% at 18 months[27]. Even in patients receiving azidothymidine (zidovudine), it appears that prophylactic or suppresive therapy is indicated[8]. Trimethoprim-sulfamethoxazole is an effective agent but side effects limits its usefulness[7]. Weekly doses of Fansidar are beneficial, but Stevens-Johnson syndrome, although uncommon, is a potentially severe complication[6, 13]. Preliminary work suggested dapsone to be a highly effective prophylactic drug[18]. Two of our patients received monthly doses of 300 mg of aerosol pentamidine, but they experienced recurrences at 2 and 7 months of prophylaxis, respectively (data not shown). However, GOLDEN et al.[11] reported that inhalatory pentamidine can reduce the frequency of relapse and the case fatality rate by 50%. Of note, the shortest interval between onset of **P. carinii** pneumonia and the previous dose of pentamidine was 18 days. Therefore, increasing the doses or frequency of inhalation might result in a further decrease in the rate of pneumocystosis.

In conclusion, inhaled pentamidine is an effective, less toxic treatment for mild and moderate cases of **P. carinii** pneumonia and is suitable for outpatient use. More studies are warranted to determine the best therapeutic dose and the ideal regimen for prophylaxis of pneumocystosis.

RESUMO

Aerosol de Pentamidina no Tratamento da Pneumonia por Pneumocystis carinii **em pacientes com a síndrome da imunodeficiência adquirida.**

O objetivo deste estudo consistiu em avaliar pentamidina inalatória para o tratamento de pneumonia leve a moderada, causada por **Pneumocystis carinii**. Oito adultos com a síndrome da imunodeficiência humana e pneumocistose (4 apresentando o primeiro episódio e 4 na vigência de pneumocistose de repetição) receberam inalações diárias de isetionato de pentamidina por 21 dias. Seis pacientes foram tratados com doses de 300 mg de pentamidina e os 2 restantes receberam 600 mg diariamente. No grupo de 300 mg, 2 indivíduos desenvolveram neutropenia leve e transitória. Porém, ambos os pacientes recebendo 600 mg de pentamidina aerosol apresentaram leucopenia. Um deles teve toxicidade importante (intolerância global de 12,5%), que levou a suspensão da droga e impediu a avaliação da sua eficácia. Entre os 7 pacientes que puderam ser avaliados, 6 (86%) completaram o tratamento com sucesso. Um paciente que recebeu 300 mg de pentamidina diariamente teve uma recorrência precoce. Em conclusão, a pentamidina inalatória representa uma modalidade terapêutica eficaz contra a pneumonia por **Pneumocystis carinii**. E menos tóxica do que as drogas usadas convencionalmente e também pode ser administrada ambulatorialmente.

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