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Clinical Pharmacology Original Article

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Low incidence of *Pneumocystis carinii* pneumonia in HIV patients receiving 300 mg pentamidine aerosol every 2 weeks

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Summary. The optimal dosage of pentamidine for prophylaxis of *Pneumocystis carinii* pneumonia (PcP) is unknown. We assessed the effects of 300 mg pentamidine inhaled every 2 weeks. Salbutamol was added for prevention of bronchoconstriction. A total of 128 consecutive HIV patients were enrolled, 21 of whom were excluded within 8 weeks; the remaining 107 patients, 66 on primary and 41 on secondary prophylaxis, were treated for 39 weeks (median; range 8–133). Two patients developed PcP. Side effects occurred in only 14 of 5082 inhalations. Three patients developed hypoglycemia after inhalations. Blood glucose levels determined in 34 patients before and after inhalation revealed a decline from 89 ± 23 mg/dl to 79 ± 23 mg/dl ($P < 0.005$). A randomized prospective trial is necessary to evaluate the efficacy of 300 mg pentamidine inhaled every 4 or 2 weeks.

Key words: HIV – *Pneumocystis carinii* – Prophylaxis – Pentamidine

The incidence of *Pneumocystis carinii* pneumonia (PcP) has significantly declined since pentamidine aerosol became available for prophylaxis in 1988. Nevertheless, up to now both the optimal dosage of pentamidine and the interval between the inhalations is unknown. In a randomized dose escalating study (30 mg inhaled every 2 weeks, 150 mg every 2 weeks, 300 mg every 4 weeks) the highest dose was related to the highest efficacy [4]. We report on the effects of 300 mg pentamidine inhaled every 2 weeks for primary and secondary prophylaxis of PcP, a dose twice as high as that used by Leoung and colleages [7].

Patients and methods

HIV-infected patients with AIDS and patients with a CD4 cell count below 250/μl were eligible. Patients on secondary prophylaxis started pentamidine inhalation at the end of a 3-week course of high-dose intravenous cotrimoxazole. A total of 128 consecutive patients were enrolled (118 men and 10 women). Pentamidine 300 mg isethionate was inhaled every 2 weeks by a Respigard II nebulizer system (Marquest, Englewood, Colorado) linked to an jet-air stream compressor (Salvia, Hamburg, FRG) with an air flow of 7 l/min. Pentamidine was dissolved in 6 ml aqua ad injectabilia. Salbutamol 1 ml (5 mg) was added for prophylaxis of bronchospasm. The patients inhaled pentamidine in the outpatient department, in a sitting position wearing a nasal clamp. They were questioned about side effects after each inhalation. To determine the effects of pentamidine aerosol on blood glucose levels, venous blood specimen were drawn immediately before and after the inhalation. An inhalation lasted about 30 min.

Abbreviation: PcP = *Pneumocystis carinii* pneumonia

Results

Within 8 weeks 21 patients were withdrawn: 19 because of non-compliance, and 2 patients died. One died 2 days after enrollment; autopsy revealed PcP, pulmonary aspergillosis, and disseminated cytomegalovirus infection. The second patient died of pulmonary aspergillosis after 7 weeks. No *Pneumocystis carinii* was detected at autopsy. Thus 107 patients were treated for at least 8 weeks and considered eligible for determining the efficacy of pentamidine inhalation. Their mean CD4 cell count was 105 ± 114/μl. Of these, 66 (62%) received primary prophylaxis and 41 (38%) secondary prophylaxis. Their characteristics are shown in Table 1.

Two patients developed PcP, confirmed by bronchoalveolar lavage. One was a 38-year-old man on secondary prophylaxis. He had suffered from a first episode of PcP 6 weeks prior to enrollment. He had been treated with cotrimoxazole intravenously for 3 weeks. On the last day of cotrimoxazol treatment prophylaxis was initiated. After 12 weeks on pentamidine inhalation PcP was diag-

Table 1. Patient's characteristics at study entry (only patients on prophylaxis for at least 8 weeks are included)

Characteristic	Primary prophylaxis ($n=66$)	Secondary prophylaxis ($n=41$)
Age (years)		
Mean	40	38
Range	23–74	24–59
CD4 count ($\times 10^9$/l)		
Mean	125	81
Range	8–739[a]	0–601[a]
Weeks on prophylaxis		
Mean	44	54
Range	8–133	12–126
Medication taken		
Zidovudine	37 (56%)	16 (39%)
Acyclovir	5 (8%)	2 (5%)
Ganciclovir	1 (2%)	2 (5%)
Pyrimethamine	5 (8%)	3 (7%)
Clindamycin	5 (8%)	3 (7%)
Ketoconazole	11 (17%)	14 (34%)
HIV-related conditions (except PcP)		
Candida esophagitis	10 (15%)	4 (11%)
CMV	2 (3%)	2 (5%)
Toxoplasmosis	5 (8%)	3 (7%)
MAI infection	4 (6%)	3 (7%)
Kaposi's sarcoma	9 (14%)	4 (11%)
Lymphoma	2 (3%)	0 (0%)
Other	9 (14%)	8 (21%)

CMV, Cytomegalovirus infection; MAI, *Mycobacterium avium/intracellulare* complex

[a] Patients with AIDS according to the criteria of the Centers for Disease Control

nosed, to which the patient succumbed 1 week later. The second was a 74-year-old man on primary prophylaxis. PcP developed after 39 weeks, being the first manifestation of full-blown AIDS. The patient was successfully treated with cotrimoxazole. Of the 107 patients 54 had to be taken off the protocol, 25 on primary and 29 on secondary prophylaxis. Of these, 46 died; there was no clinical suspicion of PcP in any of them. Eight patients were lost to follow-up. Autopsy was performed in 19 of 46 patients. *Pneumocystis carinii* was found in the lungs of one patient who had been on secondary prophylaxis for 1 year. Pentamidine inhalation had been introduced immediately after the first episode of PcP. This patient died of a cerebral hemorrhage. In the remaining 18 patients no *Pneumocystis carinii* was detected in any tissue.

Fourteen of the 128 patients reported side effects. Five complained of cough, three of dizziness, three of ravenous appetite, two of numbness of the face, and one each of nausea, dyspnea, and burning pain of the chest. One patient stopped inhalation because of a bronchospasm despite salbutamol. The other side effects were tolerable and occurred once in each patient. Thus, side effects occurred in 14 of 5082 inhalations (0.3%). The three patients with reported ravenous had blood glucose levels below 60 mg/dl. To elucidate the coincidence of hypoglycemia and inhalation of pentamidine, we determined the blood glucose levels in 34 consecutive fasting patients (Fig. 1). The mean blood glucose before inhalation was 89 ± 23 mg/dl and 79 ± 23 mg/dl after inhalation ($P < 0.005$; t test). In one patient blood glucose decreased from 102 to 49 mg/dl. After inhalation of 6 ml normal saline solution there was no substantial change of the blood glucose levels in six patients who also received pentamidine inhalation.

Discussion

Until 1988 PcP was the most common opportunistic disease and a major cause of death in HIV-infected patients. It has been estimated that about 75% of AIDS patients develop PcP at some time during their illness [5]. The incidence of PcP over 12 months is about 18% in patients with a CD4 cell count below 200/μl without prophylaxis of PcP [8].

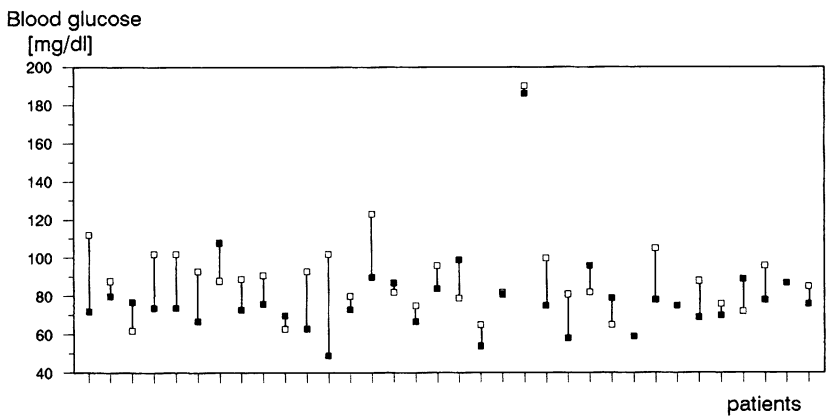

Fig. 1. Blood glucose levels in 34 consecutive patients before and after inhalation of 300 mg pentamidine. Mean blood glucose levels were 89 ± 23 mg/dl before and 79 ± 23 mg/dl after inhalation ($P < 0.005$). Three patients had identical blood glucose levels before and after inhalation; for these only one dot is shown. □, Blood glucose levels before inhalation; ■, blood glucose levels after inhalation

Only two of 107 patients (2%) developed PcP over a mean observation period of 48 weeks while on prophylaxis with 300 mg pentamidine aerosol given every 2 weeks. In another patient *Pneumocystis carinii* was detected in the lungs at autopsy without clinical signs of pneumonia. Recently the results of prophylaxis with 300 mg pentamidine administered every 4 weeks were reported [7]. Of 139 patients 16 (12%) on primary or secondary prophylaxis developed PcP over an observation period of 30 weeks (median). The mean CD4 cell count was 161/μl. When patients received the same regimen for primary prophylaxis, 6 of 114 patients (5%) developed PcP over a mean observation period of 3 months [6]; the mean CD4 cell counts were 140/μl. In contrast, only 7 of 120 patients (6%) who received 200 mg pentamidine aerosol every 2 weeks for primary or secondary prophylaxis developed PcP over a mean observation period of 9 months [9]; the mean CD4 cell count was 68/μl. The low incidence of PcP after administration of 300 mg pentamidine every 2 weeks seems remarkable. Augmentation of the volume by adding 1 ml salbutamol and an improved distribution of the aerosole in the lungs compared with application separately from the aerosole may in part account for these differences. In addition, study populations and observation periods are not identical. A randomized trial is necessary to determine whether a lower incidence of PcP can be achieved by inhalation of 300 mg pentamidine every 2 weeks. These results may be of particular interest concerning patients with a CD4 cell count below 50/μl, as these patients seem to have an increased risk of developing PcP [9].

Single administration of pentamidine aerosol results in high lung levels in rats, which do not decrease during the first 48 h after aerosolization [2]. In patients receiving daily pentamidine inhalation for treatment of PcP drug levels were determined in bronchoalveolar lavage at different time points [1]. There was no significant difference between the pentamidine concentration after 1 and 15 days of therapy, suggesting that there is no accumulation of pentamidine in the lungs. One month after completion of 2 weeks' therapy, the concentration of pentamidine in the bronchoalveolar lavage was approximately 10% of that determined during treatment. These data suggest that 2-weekly inhalation of pentamidine may result in higher drug levels in the lungs compared to 4-weekly administration, thereby reducing the incidence of PcP. Side effects occurred in 0.3% of inhalations. Cough is reported in about 30% of pentamidine inhalations [6, 7]. The extremely low occurrence of cough in our study is probably related to the routine administration of salbutamol. No side effects related to salbutamol itself were noticed. Hypoglycemia has been reported after intravenous administration of pentamidine [4]. Blood glucose levels were significantly reduced after inhalation of 300 mg pentamidine. Recently 25 patients were studied for effects of pentamidine inhalation on blood glucose levels [3]. They experienced a significant decrease in glucose levels and a simultaneous increase in serum insulin levels. To avoid this side effect patients should not be fasting when inhaling pentamidine.

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