A prospective comparison of Porta-sonic and Fisoneb ultrasonic nebulizers for administering aerosol pentamidine

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OBJECTIVE: To report patient acceptability and overall therapeutic effectiveness of two different ultrasonic nebulizers, Fisoneb and Porta-sonic, for the administration of aerosol pentamidine for *Pneumocysitis carinii* prophylaxis in human immunodeficiency virus (HIV)-infected individuals.
DESIGN: Prospective assessment of a random subgroup of 174 individuals from an inception cohort of 1093 patients attending a central aerosol pentamidine treatment centre in Toronto, Ontario.
METHODS: One hundred and seventy-four patients who had been receiving aerosolized pentamidine for more than 10 weeks using Fisoneb at 60 mg every two weeks were switched to Porta-sonic. Subjective evaluation included three standard 10 cm visual analogue scales rating cough/wheeze, aftertaste and overall preference. The individuals were also asked to compare the duration of time spent on the aerosol treatments. Objective evaluation included spirometry performed immediately before and 15 mins after pentamidine administration. Prospective surveillance of the entire cohort was preformed to record and document episodes of breakthrough *P carinii* pneumonia.
RESULTS: Porta-sonic was the overall preferred nebulizer in 82% of patients. Less time was spent on aerosol treatment using the Porta-sonic nebulizer compared with the Fisoneb in 66% of patients. The Porta-sonic nebulizer system produced less aftertaste compared with Fisoneb. Both nebulizers produced significant but modest reduction in flow rates. During the study period there was no statistically significant difference in the rates of breakthrough *P carinii* pneumonia between the two groups. A total of 91 episodes occurred, at a rate of 0.5 episodes per patient-month on Porta-sonic compared with 0.7 episodes per patient-month on Fisoneb (P=0.2536).
DISCUSSION: Aerosol pentamidine remains the proven second-line prophylaxis against *P carinii* pneumonia in HIV/AIDS for those intolerant to trimethoprim-sulphamethoxazole. Cough, bronchospasm and poor taste are side effects that may limit patient tolerance and acceptability. The results of this study show that the Porta-sonic nebulizer system significantly reduces some of these side effects and increases patient preference.
CONCLUSION: This study suggests that Porta-sonic, the newer nebulizer system, with more ideal in vitro characteristics may become a favoured device in clinical practice.

Key Words: *Human immunodeficiency virus, Nebulizers, Pentamidine,* Pneumocystis carinii *pneumonia, Prophylaxis*

continued on next page

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Comparaison prospective des nébuliseurs à ultrasons Porta-sonic et Fisoneb pour l'administration de pentamidine en aérosol

OBJECTIF : Mesurer le taux d'acceptabilité chez les patients, ainsi que l'efficacité thérapeutique globale de deux nébuliseurs à ultrasons, Fisoneb et Porta-sonic, pour l'administration de pentamidine en aérosol en prévention de la pneumonie à *Pneumocystis carinii* chez des sujets infectés au virus de l'immunodéficience acquise (VIH).

MODÈLE : Évaluation prospective d'un sous-groupe randomisé de 174 sujets provenant d'une cohorte d'inception de 1093 patients sous traitement aérosol central à la pentamidine dans un établissement de santé de Toronto, Ontario.

MÉTHODES : Cent soixante-quatorze patients qui recevaient de la pentamidine en aérosol depuis plus de 10 semaines à l'aide de l'appareil Fisoneb, à raison de 60 mg aux deux semaines, sont passés à un appareil Porta-sonic. Les mesures subjectives comprenaient trois échelles analogues visuelles de 10 cm pour évaluer la toux/les sibilances, l'arrière-goût et la préférence globale. Les sujets ont également dû comparer le temps passé en traitements aérosol. L'évaluation objective portait sur la spirométrie effectuée immédiatement avant et 15 minutes après l'administration de la pentamidine. Le suivi de la cohorte en entier a été effectué afin d'enregistrer et de documenter tout épisode de pneumonie à *P carinii*.

RÉSULTATS : Le Porta-sonic a été globalement le nébuliseur préféré de 82 % des patients. Soixante-six pour cent des patients ont passé moins de temps en traitement aérosol s'ils utilisaient le nébuliseur Porta-sonic plutôt que le Fisoneb. Le système de nébuliseur Porta-sonic a produit moins d'arrière-goût que le Fisoneb. Les deux systèmes de nébulisation ont produit moins d'arrière-goût que le Fisoneb seul. Les deux nébuliseurs ont produit une réduction modeste mais significative des débits durant la période de l'étude. Aucune différence significative au plan statistique n'a été enregistrée quant au taux de PPC entre les deux groupes. En tout, 91 épisodes sont survenus à un taux de 0,5 épisode par mois-patient avec l'appareil Porta-sonic contre 0,7 épisode par mois-patient avec le Fisoneb (P=0,2536).

DISCUSSION : La pentamidine en aérosol demeure la prophylaxie de deuxième ligne éprouvée contre la PPC en présence du VIH/SIDA pour les patients qui ne tolèrent pas le triméthoprim-sulphaméthoxazole. La toux, le bronchospasme et l'arrière-goût sont des effets secondaires qui peuvent réduire la tolérance du patient et rendre le traitement moins acceptable. Les résultats de cette étude révèlent que le système de nébuliseur Porta-sonic réduit significativement certains de ces effets secondaires et est préféré des patients.

CONCLUSION : Cette étude suggère que le Porta-sonic, le système le plus récent de nébulisation, doté de caractéristiques *in vitro* plus convenables, pourrait devenir l'appareil préféré en pratique clinique.

PNEUMOCYSTIS CARINII PNEUMONIA (PCP) IS THE MOST common opportunistic pulmonary infection in patients infected with the human immunodeficiency virus (HIV), occurring in 85% of patients at some time during their illness. Relapse after successful treatment of PCP without subsequent prophylaxis is up to 60% at one year. Each recurrence confers an increased risk for morbidity, and mortality is estimated at up to 20% with each episode of PCP.

Aerosolized pentamidine (AP) has been demonstrated in randomized controlled studies to be effective as both primary and secondary prophylaxis for PCP (1-3). Inhalation of pentamidine over one year appears to be free from systemic toxicity (2,3). However, local side effects including alteration in taste, cough and bronchospasm occur in 16 to 36% of patients as acute side effects (4). A significant proportion of HIV patients treated with AP developed bronchospasm, and spirometry reveals airflow obstruction in about 25% of subjects (5). Some investigators have proposed that the significant decline in flow rates is sufficient to treat all patients prophylactically with bronchodilator, even in the absence of symptoms (6). Some of the unpleasant acute side effects may depend on the type of nebulizer used, the dose of pentamidine and the concentration of the nebulized solution.

Several nebulizers are used throughout the world for delivering AP. Respirgard-II (Marquest, Colorado) is a high frequency, handheld, continuous flow jet nebulizer producing particles in the 1 to 2 μm diameter range which, along with the Aerotech-II (Cadema Medical Products Inc), is very popular in the United States (2). Fisoneb (Fisons, New York), a reusable low frequency ultrasonic nebulizer that delivers particles in the 2 to 5 μm diameter range, but with a much higher efficiency, is widely used in Canada (6). Throughout the world, various other versions of ultrasonic nebulizers are in use, including a relatively new ultrasonic nebulizer, Porta-sonic (DeVilbiss, Pennsylvania), which delivers particles in the 1 to 2 μm range. Because of the one-way valve design of the Porta-sonic, it is able to achieve a delivery efficiency of up to 25%, which is superior to the other nebulizers in use (7). The characteristics of the different versions of nebulizers for AP are summarized in Table 1.

To our knowledge no clinical trials have directly compared different nebulizer systems for PCP prophylaxis. This study presents new clinical information for the Porta-sonic, with the objective of finding a better tolerated nebulizer system for administering AP. Recently two important studies clearly demonstrated that trimethoprim-sulfamethoxazole (TMP-SMX) is more effective than AP for both primary (8) and secondary (9) PCP prophylaxis. However, the studies reaffirmed AP as a proven, though less effective, second-line alternative.

TABLE 1
Ultrasonic/jet nebulizer characteristics

Nebulizer	MMAD (μm)	Delivery efficiency %
Ultrasonic		
Fisoneb	2.5	10-15
Porta-sonic	1.8	25
Jet		
Aerotech-II	1.1	21
Respirgard-II	0.76	4.6

Delivery efficiency is the percentage of administered dose available at the mouth following nebulization. MMAD Mass median aerodynamic diameter

It is particularly important to continue research to attempt to maximize the efficacy of AP, as a large number of individuals are intolerant to TMP-SMX. Patients can easily continue AP therapy on a long term basis.

No studies have directly compared different nebulizer systems in vivo. It seems realistic to suggest that this first generation of nebulizer systems for AP administration may be improved on, with ultimately increased compliance, tolerability and efficiency.

PATIENTS AND METHODS

Objectives: The primary objective of this study was to assess patients' acceptance or tolerance of the currently used ultrasonic nebulizer, Fisoneb, with a newer ultrasonic nebulizer, Porta-sonic. A secondary objective was to evaluate the effectiveness of the Porta-sonic against the conventional standard, the Fisoneb.

Patient population: One hundred and seventy-four HIV patients receiving regular AP at the Toronto Central Aerosolized Pentamidine Clinic were enrolled in the study between February and March 1990. All patients were documented to be HIV-positive, 77% were receiving AP as primary prophylaxis and 23% were receiving it for secondary prophylaxis. The risk behaviour for the development of HIV was homosexual or bisexual behaviour in 96% of patients. Mean age was 39 years, and 97% of the study population were males.

Study design: This prospective study used an open crossover design, with an inception cohort of 1093 HIV-infected individuals, 174 of whom consented to switch to the Porta-sonic nebulizer.

Study protocol: All 174 participants were new patients recently established on the maintenance phase of their AP protocol (3), and they had been on regular AP administration every two weeks using the Fisoneb device for at least 10 weeks. During this time individual patients were considered to have passed through their Fisoneb learning curve and had become comfortable with nebulized treatment regimen. The AP protocol was adapted from the Canadian cooperative study (3), which consists of a loading phase of five doses at 60 mg per treatment over two weeks. The patients then undergo a 60 mg maintenance phase every two weeks.

All 174 patients who were recruited in the study agreed to participate after appropriate consent was obtained. Although all were invited, only a subgroup of 75 patients also agreed to partake in a more involved spirometric evaluation. The principal reason why the remaining 99 patients declined to participate in the spirometric evaluation was the extra time commitment required.

All patients were asked to rate the Fisoneb machine using three standard 10 cm visual analogue scales (5). Patients were then switched to the Porta-sonic device at 60 mg dissolved in 3 mL of sterile water on subsequent scheduled visits every two weeks. Porta-sonic was used for administrating AP on a minimum of two occasions before the patients were asked to evaluate that device during subsequent therapies. For the subset of 75 patients who took part in the spirometric evaluation, spirometry was performed pre- and post-AP to document any changes in the flow rates before switching to Porta-sonic, and spirometric studies were repeated while on Porta-sonic.

Subjective assessment: Subjective evaluation was conducted using three 10 cm visual analogue scales validated in a similar patient population in prior studies (5). Patients were asked to rate the severity of cough/wheezing and aftertaste using a 10 cm visual analogue scale, with the 0 cm mark labelled as none and the 10 cm mark labelled as severe. They were also asked to rate the overall performance of the machines for administering AP, again with the 0 cm mark labelled as totally unsatisfactory, and the 10 cm mark labelled as highly satisfactory. Time spent in the AP adminstration was also rated by the patient using a categoric scale labelled as less, about the same, or more to compare Porta-sonic with Fisoneb.

Objective assessment: Spirometry was performed by a single respiratory technician before and after AP using the same computerized pulmonary function test equipment (Collins 03000, WE Collins Inc, Massachusetts). At least three spirometric attempts were performed and the best value was recorded.

Breakthrough episodes of PCP: Prospective surveillance of the entire cohort of 1093 HIV-infected individuals was performed to detect episodes of breakthrough PCP.

Data analysis: Continuous variables such as visual analogue scale scoring and spirometric results were expressed as means plus or minus standard deviations, and the results of the two groups were compared using paired Student's *t* test. For categoric variables such as breakthrough episodes of PCP, χ^2 statistic was used.

A two-tailed P value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

In terms of subjective evaluation (Table 2), the results from the 174 patients indicated that the Porta-sonic nebulizer was associated with less cough/wheezing and aftertaste, with a mean rating of 3.41 and

TABLE 2
Subjective assessments of Fisoneb and Porta-sonic

	Fisoneb	Porta-sonic	P value
Number of patients	174	174	
Cough/wheezing	3.71±2.72	3.41±3.01	0.546*
Aftertaste	5.23±2.67	3.67±2.94	0.0001†
Overall rating	6.63±2.11	8.30±1.85	0.0001†
Nebulizer of choice	32 (18%)	142 (82%)	0.001†
Duration of treatment using Porta-sonic compared with Fisoneb			0.0001†
Shorter		66%	
Same		21%	
Longer		13%	

*Results are expressed as mean ± SD. *Student's t test two-tailed; †χ^2. Rating scales were as follows: for coughing/wheezing and aftertaste, 0=none, 10=severe; for overall rating, 0=completely unsatisfactory, 10=highly satisfactory*

TABLE 3
Spirometric assessments of Fisoneb and Porta-sonic

	Fisoneb	Porta-sonic	P value
Number of patients	75	75	
Number of smokers (%)	19 (25%)	20 (27%)	0.8528*
Pretreatment FVC (%)	95±16	95±16	0.477†
Post-treatment FVC (%)	92±17	93±17	0.172†
Pretreatment FEV_1 (%)	92±17	93±17	0.405†
Post-treatment FEV_1 (%)	87±17	88±17	0.32†

*Results are expressed as mean ± SD of percentages of predicted values. FVC Forced vital capacity; FEV_1 Forced expiratory volume in 1 s; *χ^2; †Student's t test paired two-tailed*

TABLE 4
Breakthrough episodes of *Pneumocystis carinii* pneumonia

	Porta-sonic	Fisoneb
Number of patients	174	983
Mean number of months (range)	11 (6-21)	10 (1-35)
Patient-months	2501	10,749
Episodes BPCP	12	79
% episodes BPCP/ patient-month	0.5	0.7

BPCP Breakthrough Pneumocystis carinii *pneumonia.* $\chi^2=1.303$; *P=0.2536*

3.67 visual analogue scale, respectively. The cough/wheezing rating using the Fisoneb (3.71) was not significantly higher than the rating for Porta-sonic. The mean aftertaste rating using the Fisoneb, at 5.23, was significantly higher than the rating using Porta-sonic (P=0.0001). Porta-sonic was rated higher in terms of overall satisfaction using the device. Time taken to administer an AP treatment was shorter using the Porta-sonic in two-thirds of the patients, compared with the duration of previous treatments using Fisoneb. The Porta-sonic was rated as the overall preferred device by 82% of users (P=0.001) (Table 2).

The comparable frequency of cough/wheeze based on subjective assessment using the visual analogue scale with Fisoneb and Porta-sonic was confirmed by the objective spirometric data. Although both devices precipitated a significant reduction in forced vital capacity and forced expiratory volume in individual patients, this reduction was similar with either the Porta-sonic or Fisoneb machine (Table 3).

Prospective surveillance of the cohort of 1093 HIV-infected individuals detected 91 breakthrough episodes of PCP: 12 in patients receiving prophylaxis via Porta-sonic and 79 in patients receiving prophylaxis via Fisoneb. There were no episodes of extrapulmonary pneumocystosis. Table 4 outlines the number of individuals on each treatment regimen, the mean number of months on that system and the total number of patient-months of treatment with each nebulizer system. The percentage of episodes of breakthrough PCP/patient-month is 0.5 for Porta-sonic and 0.7 for Fisoneb ($\chi^2=1.303$, P=0.2536).

DISCUSSION

PCP remains a major concern among HIV patients in the 1990s. The demonstration of AP as an effective means of prophylaxis for PCP has led to large scale use of AP as primary and secondary prophylaxis of PCP. Even though the long term usage of AP appears to be safe, the acute pulmonary toxicity of AP is an area of ongoing concern. Bronchospasm and aftertaste caused by AP administration enhances patient discomfort during treatment, which may lead to poor compliance. Moreover, bronchospasm may exacerbate tendency towards nonuniform aerosol distribution of AP (10), which may theoretically account for some of the breakthrough episodes of PCP despite AP prophylaxis. Thus, the assessment of newer nebulizers is highly desirable.

Many newer ultrasonic nebulizer systems are being developed with perhaps more ideal delivery characteristics from in vitro experiments (11,12). However, these theoretical advantages must be studied in the appropriate clinical settings.

Although a randomized double-blind clinical trial is the ideal, this was not deemed possible in our situation, for a number of reasons. The only way blinding could have been obtained would have been by setting up the nebulizer (Fisoneb or Porta-sonic) sealed in a black box to hide the identity, with additional tubing to allow inhalation. This tubing would have altered the nebulizer and particle characteristics and would have invalidated the study.

We were also uncertain of the effectiveness of this new nebulizer and specifically elected to invite patients to participate in this study only after they had received their five loading doses of 60 mg pentamidine via Fisoneb over a two-week period. Therefore, patients were only enrolled during the maintenance phase of therapy.

The results of this study – comparing two ultrasonic nebulizers with different aerosol particle size production and delivery efficiency using the same dose and concentration of pentamidine – establish evidence for patients' acceptance or tolerance of different nebulizers. To our knowledge, this is the first clinical trial attempting to correlate in vitro nebulizer assessments with practical patient management. Smaldone et al (12) showed that the major factor influencing pentamidine deposition was aerosol delivery, and this was dependent on the inherent characteristics of individual nebulizers.

The results of our study confirm that the newer ultrasonic nebulizer, Porta-sonic – which generates an aerosol of smaller particle size (mass median aerodynamic diameter 1.8 μm) and greater delivery efficiency of 25% (7) – is associated with less aftertaste and less time spent on AP administration, and was the nebulizer preferred by the majority of patients. The Fisoneb device (mass median aerodynamic diameter 2.5 μm, delivery efficiency 15%) (9) is associated with more problems with aftertaste and was less preferred by patients. Despite the smaller particle size generated by Porta-sonic, there is no significant difference in the flow rate reduction compared with Fisoneb. There is no significant difference in the number of episodes of breakthrough PCP occurring with administration by either the Fisoneb or Porta-sonic system (P=0.2536) (Table 4).

The results of this study support the therapeutic effectiveness of Porta-sonic and demonstrate that this promising new device is well tolerated and accepted by patients. The smaller particle size of the Porta-sonic may enhance more even distribution throughout the lung zone (10), and the higher efficiency may also minimize the potential of environmental spillover of pentamidine (13). One should not undervalue the importance of subjective evaluation by patients for what may be perceived to be a relatively minor side effect such as aftertaste, cough/bronchospasm, duration of treatment and overall preference. The validity of the visual analogue scale, which we have used to asses patient tolerability and side effects in previous studies on aerosol pentamidine, was confirmed in this study by concurrence of the objective ratings from pulmonary function test and the visual analogue assessment of the patients. The most important factors in achieving long term success of PCP prophylaxis using AP are continued patient acceptance and high level of compliance. The results of this study support further investigation to establish the effectiveness of Porta-sonic in administering AP for the prophylaxis of PCP. With its high delivery efficiency, it may be possible to administer a single dose of 60 mg per month via Porta-sonic, which would reduce the cost of administering AP substantially.

As time progresses and the number of breakthrough episodes of PCP increases, it becomes imperative to ascertain the most user-friendly and cost-effective method of pentamidine delivery.

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REFERENCES

1. Hirschel B, Lazzarin A, Chopard P. A controlled study of inhaled pentamidine for primary prevention of *Pneumocystis carinii* pneumonia. N Engl J Med 1991;324:1079-83.
2. Leoung GS, Feigal DW, Montgomery AB, et al. Aerosolized pentamidine for the prophylaxis against *Pneumocystis carinii* pneumonia. N Engl J Med 1990;323:769-75.
3. Montaner JSG, Lawson LM, Gervais A, et al. A placebo-controlled study of aerosol pentamidine for the secondary prophylaxis of AIDS-related PCP. Ann Intern Med 1991;114:948-53.
4. Toronto Aerosolized Pentamidine Study (TAPS) Group. Acute pulmonary effects of aerosolized pentamidine. A randomized controlled study. Chest 1990;98:907-10.
5. Katzman M, Meade W, Iglar K, Rachlis A, Berger P, Chan CK. High incidence of bronchospasm with regular administration of aerosolized pentamidine. Chest 1992;101:79-81.
6. Montaner JSG, Hunter J, Pare PD. Aerosolized pentamidine induced bronchospasm and its response to therapy. Am Rev Respir Dis 1990;141:A268.
7. Smalldone GC, Perry RJ, Deutsch DG. Characteristics of nebulizers used in the treatment of AIDS related *Pneumocystis carinii* pneumonia. J Aerosol Med 1988;1:113-26.
8. Schneider MME, Hoepelman AIM, Eeftinck Schatenkerk JKM, et al. A controlled trial of aerosolized pentamidine or trimethoprim sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. N Engl J Med 1992;327:1836-41.
9. Hardy WD, Feinberg J, Finklestein D, Power ME, He W, Koczka C. ACTG Protocol 021. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome. N Engl J Med 1992;327:1842-8.
10. Simonds AK, Newman SP, Johnson MA. Factors determining regional deposition of aerosolized pentamidine. Am Rev Respir Dis 1990;141:A269.
11. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC. Nebulizer function during mechanical ventilation. Am Rev Respir Dis 1992;145:1117-22.
12. Smaldone GC, Fuhrer J, Steigbigel RJ, McPeck M. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1991;143:727-37.
13. McIvor RA, Rachlis A, Berger P, Bonner M, Lee Pack LR, Chan CKN. Risk of second hand exposure to aerosol pentamidine. J Aerosol Med 1992;5:11-7.