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

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ORIGINAL ARTICLE


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 Pneumocystis 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 performed 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
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 carini* chez des sujets infectés au virus de l’immunodéficience acquise (VIH).

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

**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 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 PCP 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 PCP en présence du VIH/SIDA pour les patients qui ne tolèrent pas le triméthoprilm sulfaméthoxazole. 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 conformables, pourrait devenir l’appareil préféré en pratique clinique.
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 administering 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/wheezeing 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 administration 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, $\chi^2$ 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/wheezeing and aftertaste, with a mean rating of 3.41 and
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, 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.

### TABLE 2
Subjective assessments of Fisoneb and Porta-sonic

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

Results are expressed as mean ± SD. *Student's t test two-tailed; †$\chi^2$; ‡Student's t test paired two-tailed.

### TABLE 3
Spirometric assessments of Fisoneb and Porta-sonic

<table>
<thead>
<tr>
<th></th>
<th>Fisoneb</th>
<th>Porta-sonic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>75</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Number of smokers (%)</td>
<td>19 (25%)</td>
<td>20 (27%)</td>
<td>0.8528*</td>
</tr>
<tr>
<td>Pretreatment FVC (%)</td>
<td>95±16</td>
<td>95±16</td>
<td>0.477†</td>
</tr>
<tr>
<td>Post-treatment FVC (%)</td>
<td>92±17</td>
<td>93±17</td>
<td>0.172†</td>
</tr>
<tr>
<td>Pretreatment FEV₁ (%)</td>
<td>92±17</td>
<td>93±17</td>
<td>0.405†</td>
</tr>
<tr>
<td>Post-treatment FEV₁ (%)</td>
<td>87±17</td>
<td>88±17</td>
<td>0.32†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD of percentages of predicted values. FVC Forced vital capacity; FEV₁ Forced expiratory volume in 1 s; $\chi^2$: Student's t test two-tailed.

### TABLE 4
Breakthrough episodes of Pneumocystis carinii pneumonia

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

BPCP Breakthrough Pneumocystis carinii pneumonia: $\chi^2=1.303; P=0.2536$
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 according to the inherent characteristics of individual nebulizers.

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, during treatment and overall preference. The validity of the visual analogue scale, which we have used to assess 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