

Which apparatus for inhaled pentamidine? A comparison of pulmonary deposition *via* eight nebulisers

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Which apparatus for inhaled pentamidine? A comparison of pulmonary deposition via eight nebulisers. S.H.L. Thomas, M.J. O'Doherty, C.J. Page, T.O. Nunan, N.T. Bateman.

ABSTRACT: Aerosolised pentamidine 300 mg in 5 or 6 ml solution was administered *via* 8 different nebuliser systems to 12 patients with acquired immunodeficiency syndrome. Using ^{99m}Tc human serum albumin as an indirect marker for pentamidine, pulmonary, extrapulmonary (gastric and oropharyngeal) and alveolar deposition of pentamidine were measured using a gamma camera. Side effects (visual analogue scales) and changes in lung function associated with each treatment were also quantified. Deposition was completed more rapidly with the ultrasonic than the jet nebulisers. Mean total pulmonary depositions ($\text{mg} \pm \text{SEM}$) were Respigard II, 6.1 ± 0.5 ; Centmist, 7.3 ± 1.0 ; System 22 Mizer, 14.3 ± 2.1 ; System 22 Mizer with particle separator; 4.5 ± 0.4 ; System 22 Mizer with Optimist 2, 6.3 ± 0.9 ; Fisoneb, 6.0 ± 1.2 ; Pentasonic (Portasonic); 4.6 ± 0.9 ; Samsonic, 2.9 ± 0.4 . Differences between the nebulisers for peripheral lung and alveolar deposition reflected this pattern. Side effects scores were largest with System 22 Mizer, Pentasonic (Portasonic), and Fisoneb, and these produced the greatest oropharyngeal and gastric deposition. The largest reductions in lung function were associated with System 22 Mizer. A 300 mg dose of pentamidine nebulised *via* Respigard II is known to be effective prophylaxis for *Pneumocystis carinii* pneumonia when given once monthly. Our results show that equivalent pulmonary deposition can be produced by other nebulisers. System 22 Mizer gives over twice the deposition associated with Respigard II, and used with a pentamidine dose of 150 mg is likely to produce an adequate lung dose for prophylaxis. This nebuliser, however, is associated with more marked side effects.

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Several studies have demonstrated that regularly inhaled aerosolised pentamidine is effective for preventing *Pneumocystis carinii* pneumonia (PCP) in patients with the acquired immunodeficiency syndrome (AIDS) [1-4], but the optimum dose of pentamidine and method of inhalation remains to be established [5]. Many centres use pentamidine in a dose of 300 mg monthly given *via* the Respigard II nebuliser, because this regimen is recommended by the United States Food and Drugs administration (FDA). It is more effective in preventing PCP than doses of 150 mg or 30 mg twice monthly given *via* the same nebuliser [6]. Although Respigard II produces small particles and is well tolerated, the apparatus is comparatively inefficient in depositing pentamidine within the lungs [7-8]. Other nebulisers may produce greater pulmonary deposition, but cause more severe local side effects [7-8]. If the nebulised dose could be reduced while at the same time delivering the same dose to the lung then side effects might be less severe [5].

In this study the pulmonary deposition of a nebuliser dose of 300 mg pentamidine was measured when given *via* a variety of nebulisers using ^{99m}Tc colloidal human serum albumin (^{99m}Tc HSA) as an indirect marker for pentamidine [9]. As well as determining the total pulmonary deposition and distribution of pentamidine within the lungs, the retention of marker 24 h after inhalation was also measured as it has been suggested that this represents pentamidine deposited at the site of disease beyond the mucociliary apparatus and within the alveoli, the so-called 'alveolar fraction' [10-12]. The adverse effects caused by each nebuliser were also quantified as the tolerability of each nebuliser will be a major factor in determining patient compliance.

Methods

Pulmonary pentamidine deposition was measured in 12 male patients with AIDS, of whom 8 had previously

had one or more acute episodes of PCP. Each patient gave informed consent prior to taking part in the study which was approved by the Ethics Committee of West Lambeth Health District.

In the first instance a randomised-order crossover study was performed comparing 7 nebulisers with all the patients being studied using each of the nebulisers. There were 4 jet nebulisers, Respirgard II (Marquest), Centimist (Marquest) fitted with the Respirgard II nebuliser unit, System 22 Mizer (Medic-Aid UK), System 22 Mizer modified by a custom-built particle separator [13] interspersed between the nebuliser unit and the aerosol storage chamber ('Mizer/Separator'). These nebulisers were driven by compressed air from an AFP medical air compressor which produces a static pressure of 40 psi, and a flow rate of $7.2 \text{ l}\cdot\text{min}^{-1}$ at a pressure of 15.5 psi through a standard Acorn nebuliser. The other 3 were ultrasonic nebulisers, Pentasonic (also called Portasonic in some countries, DeVilbiss), Samsonic (DP Medical) run at setting '6', and Fisoneb (Fisons) run at the lowest output setting. Low resistance filters (Pall Ultipore) were attached to each of the nebulisers not already supplied with suitable filters, to prevent the escape of pentamidine aerosol into the room. For Pentasonic (Portasonic) and Fisoneb this required the addition of a T piece (additional deadspace 15 ml) to the nebuliser mouthpiece. Studies were not performed double blind, as this was impractical, but the patients were not told the name of the equipment they were using, and the apparatus was largely concealed by lead sheeting used to screen the patient from the radioactivity within the nebuliser.

A commercially available particle separator for the System 22 Mizer, the Optimist 2 (Medic-Aid UK), became available during the later stages of the study. Pulmonary pentamidine deposition was studied in 8 of the patients using the modification after completion of the original study. Only 3 of these patients were willing to return for measurement of 24 h alveolar retention.

The particle sizes produced by each of these nebulisers were measured using a Malvern Master laser particle size and model independent calculations.

The method of measuring pentamidine deposition has been described in detail elsewhere [7-8]. On each occasion nebulised salbutamol 5 mg in 3 ml saline was administered prior to pentamidine inhalation, and spirometry (FEV_1 , FVC, PEF) measured before and after the salbutamol, and after the inhalation of pentamidine aerosol. The nebuliser solution consisted of 300 mg pentamidine and 37 MBq ($16 \text{ mcg}\cdot\text{m}^{-1}$) $^{99\text{m}}\text{Tc}$ colloidal human serum albumin ($^{99\text{m}}\text{TcHSA}$, Venticoll) in total volume of 6 ml (5 ml for Pentasonic/Portasonic). Previous research has shown that the addition of this marker does not affect the particle size or mass output of the nebulisers, and is distributed in the aerosol cloud in a similar manner to pentamidine [9-14]. The patients remained seated for the 40 min period of aerosol inhalation and were asked to breathe normally through the mouthpiece while dynamic posterior scans were taken of the lungs in 15 sec counting

frames using a gamma camera (large field of view IGE Maxi II) with a high sensitivity collimator. On completion of inhalation further static scans of the lungs (anterior and posterior), abdomen (anterior and posterior), oropharynx (right lateral head), and inhalation apparatus were acquired over 100 secs. Activity contained within the nebuliser unit was measured before and after the inhalation using the gamma camera. This was also measured using an ionisation chamber for the jet nebulisers which, unlike the ultrasonic, were small enough to fit in the chamber. On one occasion for each subject posterior and anterior ^{133}Xe scans were performed. The lung outline was defined using the 20% maximum count contour, but the mediastinal area was avoided so that counts located in the oesophagus did not contribute to measured pulmonary activity. Regions of interest were defined by dividing the lungs into 3 parts of equal height (upper, middle, and lower zones), and into central (defined as a rectangle over the middle third of the medial border of the lung and extending half way across the lung) and peripheral regions (remainder of the lung). The patients reattended the day after aerosol inhalation when further scans of the lungs were performed for the estimation of alveolar retention. This was calculated by dividing the counts detected in the lungs 24 h after aerosol inhalation, corrected for decay, by the counts detected immediately after inhalation.

Absolute pulmonary deposition was calculated using corrections derived from lung phantom studies as previously described [8,15]. Regional deposition in the lungs was corrected for differences in regional lung volumes by using the geometric means of counts derived from the posterior and anterior ^{133}Xe scans. The penetration index was calculated as $(\text{central } ^{99\text{m}}\text{Tc HSA} / \text{peripheral } ^{99\text{m}}\text{Tc HSA}) / (\text{central } ^{133}\text{Xe} / \text{peripheral } ^{133}\text{Xe})$, and the vertical distribution of pentamidine was estimated using a similar ratio comparing deposition in the upper and lower lung zones, i.e. $(\text{upper } ^{99\text{m}}\text{Tc HSA} / \text{lower } ^{99\text{m}}\text{Tc HSA}) / (\text{upper } ^{133}\text{Xe} / \text{lower } ^{133}\text{Xe})$. Only the right lung was used for estimations of regional deposition since this avoids any possible contribution from aerosol deposited in the oesophagus and stomach.

The side effects associated with each treatment were assessed using 5 separate visual analogue scales. Each of these consisted of a horizontal line 6.5 cm in length, and at each end of this line the extremes of these symptoms were printed. The 5 scales used were 'no breathlessness' - 'extreme breathlessness', 'no nausea' - 'severe nausea', 'No burning' - 'extreme burning', 'pleasant taste' - 'very unpleasant taste', and the overall impression of the treatment, 'very pleasant' - 'extremely unpleasant'. Patients were asked to place a vertical line at the point on the scale that they thought was appropriate, and this position was expressed as a percentage of the line length with higher values indicating more severe side effects.

Visual analogue scale results were analysed using the non-parametric Wilcoxon signed rank test. Pulmonary deposition results were compared using a repeated measures analysis of variance (ANOVA).

Table 1. – Nebuliser particle size outputs in the presence and absence of ^{99m}Tc HSA (Venticoll). Mass median diameters and spans shown in μm

	Without ^{99m}Tc HSA		With ^{99m}Tc HSA	
	MMD	Span	MMD	Span
Respirgard II	2.1	1.8	2.3	1.9
Centimist	2.2	1.9	2.5	1.9
System 22 Mizer	5.1	2.1	4.6	2.4
Mizer/Separator	1.6	1.8	1.9	1.9
Mizer/Optimist 2	2.1	2.0	2.2	2.1
Portasonic	4.7	1.7	4.9	1.8
Samsonic	4.6	2.0	4.6	2.0
Fisoneb	5.2	1.4	5.1	1.4

Results

The particle size outputs of each of the nebulisers are shown in table 1. Particles with the smallest mass median diameter (MMD) were produced by Respirgard II, Centimist, the Mizer/Separator, and the Mizer/Optimist 2, while larger particles were produced by Samsonic, System 22 Mizer, Fisoneb, and Pentasonic/Portasonic. The addition of ^{99m}Tc HSA to the pentamidine solution did not have a significant effect on MMD or span. These results are consistent with our previously reported data for Respirgard II and System 22 Mizer, which also showed that similar particle sizes were produced by these nebulisers using reduced pentamidine concentrations [9].

Pulmonary deposition of pentamidine is shown in table 2. Total, peripheral, and upper lung deposition was greatest using System 22 Mizer which deposited twice that of Respirgard II, Centimist, Mizer/Separator, Mizer/Optimist 2, Pentasonic/Portasonic, and Fisoneb ($p < 0.05$). The Samsonic produced less pulmonary deposition than all the other nebulisers, including Respirgard II ($p < 0.05$). The influence of the particle size output of each nebuliser is seen in the alveolar retention, which was larger for those nebulisers producing small particles, and in the penetration index (Xenon corrected central/peripheral deposition ratio) which was closest to unity (closer to the distribution of Xenon) for these nebulisers (table 2). However if alveolar deposition is calculated in absolute terms as the product of total deposition and alveolar fraction, the largest alveolar deposition was associated with System 22 Mizer, which produced more than twice that seen with Respirgard II (table 2). The upper/lower deposition ratio, corrected for differences in regional volumes using the ^{133}Xe counts, was less than unity with all the nebulisers, indicating preferential aerosol deposition in the lower part of the lung.

Dynamic aerosol deposition, for the eight systems, is shown in Fig. 1. Deposition was completed within 15 mins for the ultrasonic nebulisers, while about 35 mins was required for System 22 Mizer and the Mizer/Separator, and even after 40 mins deposition was not completed using Respirgard II, Centimist, and Mizer/Optimist 2. The effect of pentamidine inhalation on spirometry is shown in table 3. Small reductions in FEV_1 , FVC and PEFR were observed. These were largest for

Table 2. – Pulmonary deposition of 300 mg pentamidine when administered via 8 different nebulisers

	Respirgard II	Centimist	System 22 Mizer	Mizer/Separator	Mizer/Optimist 2	Fisoneb	Portasonic	Samsonic
Pulmonary deposition (mg)								
Total	6.1 \pm 0.5	7.3 \pm 1.0	14.3 \pm 2.1*	4.5 \pm 0.4	6.4 \pm 0.9	6.0 \pm 1.2	4.6 \pm 0.9	2.9 \pm 0.4*
Left lung	2.8 \pm 0.2	3.3 \pm 0.3	6.5 \pm 1.0*	2.0 \pm 0.2	2.9 \pm 0.4	3.4 \pm 0.7	2.0 \pm 0.4	1.3 \pm 0.2*
Right lung	3.3 \pm 0.3	4.0 \pm 0.5	7.8 \pm 1.2*	2.5 \pm 0.2	3.5 \pm 0.5	2.6 \pm 0.5	2.5 \pm 0.5	1.6 \pm 0.2*
Regional deposition (right lung mg)								
Peripheral	2.6 \pm 0.2	2.9 \pm 0.4	5.5 \pm 0.9*	1.9 \pm 0.2	2.7 \pm 0.4	2.4 \pm 0.5	1.8 \pm 0.4	1.1 \pm 0.2*
Central	0.45 \pm 0.06	0.53 \pm 0.10	1.47 \pm 0.26*	0.32 \pm 0.10	0.45 \pm 0.09	0.60 \pm 0.15	0.43 \pm 0.10	0.24 \pm 0.04*
Upper	0.64 \pm 0.07	0.69 \pm 0.10	1.32 \pm 0.24*	0.42 \pm 0.04	0.61 \pm 0.09	0.61 \pm 0.14	0.42 \pm 0.09	0.28 \pm 0.0*
Lower	1.3 \pm 0.1	1.5 \pm 0.2	2.8 \pm 0.5*	0.96 \pm 0.09	1.37 \pm 0.18	1.1 \pm 0.2	0.91 \pm 0.20	0.58 \pm 0.08*
Alveolar deposition								
Alveolar fraction (%)	61 \pm 2	63 \pm 4	54 \pm 3	71 \pm 6	(82 \pm 0.17)**	53 \pm 2	54 \pm 2	65 \pm 4
Alveolar deposition (mg)	3.7 \pm 0.3	4.3 \pm 0.6	7.6 \pm 1.5*	3.0 \pm 0.3	(5.3 \pm 2.1)**	3.1 \pm 0.8	2.1 \pm 0.4	1.7 \pm 0.2*
Deposition ratio's (Xe corrected)								
Central/Peripheral	1.20 \pm 0.12	1.28 \pm 0.19	1.89 \pm 0.24*	1.29 \pm 0.10	1.17 \pm 0.11	1.57 \pm 0.22	1.70 \pm 0.18	1.44 \pm 0.16
Upper/Lower	0.65 \pm 0.03	0.64 \pm 0.05	0.70 \pm 0.06*	0.65 \pm 0.05	0.60 \pm 0.04	0.76 \pm 0.06	0.61 \pm 0.03	0.71 \pm 0.04

* Significantly different from Respirgard II ($p < 0.05$) by ANOVA. ** 24 h aerosol retention data only available for 3 patients with the Mizer-Optimist 2. Results are means for 12 patients \pm SEM, except the Mizer-Optimist 2 for which $n=8$.

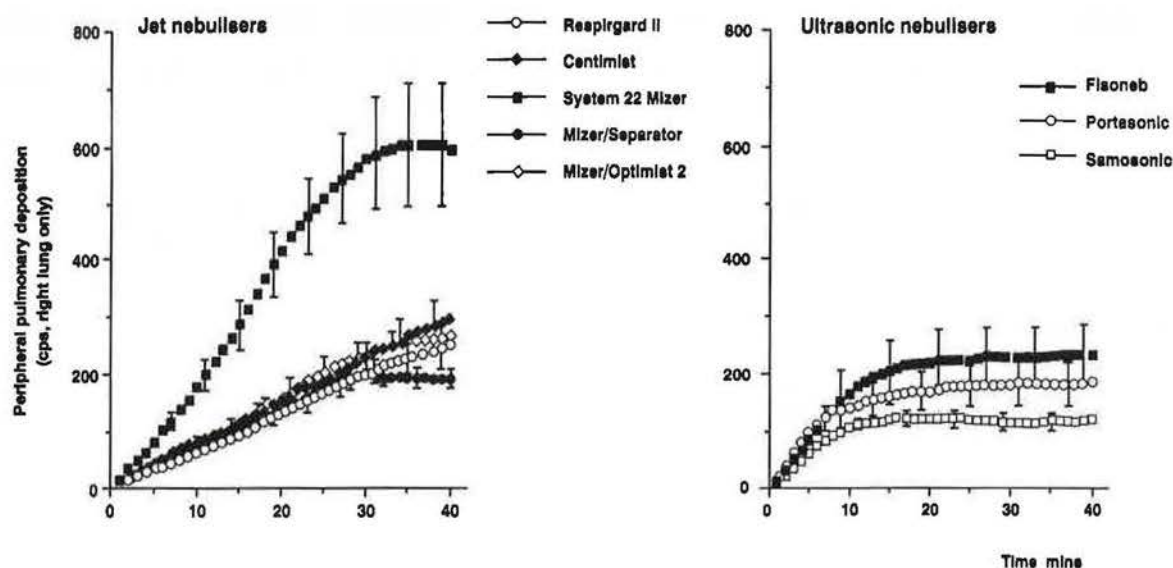


Fig. 1. — Dynamic deposition of radioaerosol in right peripheral lung *via* jet (left panel) and ultrasonic (right panel) nebulisers. Mean values \pm SEM.

Table 3. — Effects of aerosolised pentamidine on lung function when administered *via* 8 different nebulisers

	FEV ₁ l	FVC l	PEFR l·min ⁻¹
Before pentamidine			
Before salbutamol	3.24 \pm 0.61	3.81 \pm 0.65	467 \pm 121
After salbutamol	3.31 \pm 0.60	3.88 \pm 0.69	479 \pm 124
After pentamidine <i>via</i>			
Respirgard II	3.10 \pm 0.50	3.65 \pm 0.49	437 \pm 131
Centimist	3.22 \pm 0.58*	3.84 \pm 0.70*	419 \pm 117
System 22 Mizer	2.79 \pm 0.47	3.33 \pm 0.57	393 \pm 67
Mizer/Separator	3.23 \pm 0.62*	3.81 \pm 0.67*	456 \pm 117
Mizer/Optimist 2	3.33 \pm 0.70*	3.77 \pm 0.59*	524 \pm 75*
Fisoneb	3.22 \pm 0.68*	3.59 \pm 0.64	465 \pm 108*
Pentasonic (Portasonic)	3.13 \pm 0.58	3.67 \pm 0.66	449 \pm 118
Samsonic	3.09 \pm 0.65	3.56 \pm 0.58	454 \pm 101

* $p < 0.05$ vs System 22 Mizer by ANOVA. Results are mean \pm SD.

Table 4. — Side-effects associated with aerosolised pentamidine inhalation assessed using visual analogue scales. Possible values range between 0 and 100, with higher numbers indicating more marked side-effects

	Respirgard II	Centimist	System 22 Mizer	Mizer/Separator	Mizer/Optimist 2	Fisoneb	Portasonic	Samsonic
Breathlessness	9 \pm 5	11 \pm 4	35 \pm 8*	5 \pm 2	6 \pm 1	11 \pm 3	30 \pm 8	19 \pm 7
Nausea	8 \pm 5	9 \pm 2	32 \pm 8	4 \pm 1	10 \pm 6	22 \pm 10	40 \pm 10*	11 \pm 5
Burning	8 \pm 2	21 \pm 7	62 \pm 5*	10 \pm 6	16 \pm 10	45 \pm 10	63 \pm 8	17 \pm 9
Taste	34 \pm 5	52 \pm 5	70 \pm 18*	15 \pm 4	19 \pm 7	61 \pm 8*	73 \pm 7*	30 \pm 8
Overall impression	31 \pm 5	39 \pm 7	71 \pm 5*	11 \pm 3	29 \pm 9	47 \pm 7	70 \pm 6*	30 \pm 7

* $p < 0.05$ vs Respirgard II by Wilcoxon rank sum test. Mean % values \pm SD.

Table 5. — Activity in the nebuliser before and after nebulisation, and aerosol deposition in sites other than the lungs (cps \pm SEM)

	Respirgard II	Centimist	System 22 Mizer	Mizer/ Separator	Mizer/ Optimist 2	Fisoneb	Portasonic	Samsonic
Nebuliser apparatus counts								
Pre nebulisation	21143 \pm 725	21260 \pm 548	21428 \pm 492	20853 \pm 595	19883 \pm 409	20777 \pm 597	20223 \pm 408	20342 \pm 469
Post nebulisation	15699 \pm 501	15514 \pm 626	14745 \pm 642	17271 \pm 642	15720 \pm 563	18001 \pm 628	16894 \pm 737	18753 \pm 584
Nebulised activity	5445 \pm 450	5746 \pm 296	6682 \pm 689	3582 \pm 749	4163 \pm 441	2775 \pm 629	3329 \pm 786	1589 \pm 485
Nonpulmonary deposition								
Oropharynx	51 \pm 9	74 \pm 14	152 \pm 39*	22 \pm 5	59 \pm 41	70 \pm 17	37 \pm 9	39 \pm 7
Stomach	59 \pm 23	96 \pm 24	457 \pm 90*	15 \pm 5	21 \pm 5	358 \pm 99*	226 \pm 59*	64 \pm 16
Exhalant filter	4319 \pm 484	1649 \pm 270	3004 \pm 402	1451 \pm 158	1487 \pm 317	1258 \pm 290	863 \pm 255	1229 \pm 258

*: $p < 0.05$ vs Respirgard II by ANOVA.

System 22 Mizer and were significantly greater for this nebuliser than for several other nebulisers. None of the changes in lung function were associated with significant respiratory symptoms.

The results of the assessment of side effects using visual analogue scales demonstrated that the nebulisers producing the largest particles, System 22 Mizer, Pentasonic (Portasonic), and Fisoneb, produced the greatest side effects (table 4). These were related to the amount of oropharyngeal, gastric, and central pulmonary deposition associated with each nebuliser (table 5).

Discussion

Current evidence suggests that aerosolised pentamidine is effective in preventing episodes of acute PCP both in patients with AIDS who have previously had acute PCP [1–4] and in those with profound immune deficiency [16]. The number of patients who may benefit from this therapy is very large, but aerosolised pentamidine will be ineffective if delivery to the peripheral lung is inadequate, therefore it is important that the necessary data be made available so that firm and informed recommendations can be made on the optimum method for administration. The apparatus used to administer pentamidine should produce adequate pulmonary deposition for the prevention of acute PCP using the smallest dose of pentamidine inhaled over the shortest time and causing the least local side effects. The equipment should be inexpensive and suitable for use both in hospital and in the patients home.

In this study we have measured the pulmonary deposition of a nebuliser dose of 300 mg pentamidine in a total volume of 5–6 ml. This dose is approved by the United States Food and Drugs Administration, who also specify use of the Respirgard II. The total volume of 5–6 ml nebuliser fluid was selected as we have previously shown that this produces greater nebuliser output and pulmonary deposition than a 3 ml nebuliser fill while causing fewer local side effects [8].

Eight nebulisers have been assessed in this study, and all can be used in the home. Respirgard II, Pentasonic (Portasonic), and Fisoneb have been used in clinical trials which suggest that they are effective for administering pentamidine prophylaxis [5, 16, 17], although a lower (60 mg) dose was used with Fisoneb [17]. System 22 Mizer has superior deposition characteristics at lower pentamidine doses but causes more local side effects [7, 8]. Reduction of the particle size output using an impinger is expected to reduce side effects at the expense of reduced pulmonary deposition. The Centimist apparatus was used with the Respirgard II nebuliser unit as this incorporates an aerosol storage chamber and this may have the effect of increasing pulmonary deposition [18]. The Samsonic is an alternative ultrasonic device which produces comparatively small particles and has an increased nebuliser solution capacity.

As well as measuring total and peripheral pulmonary pentamidine deposition, we have also measured 'alveolar' deposition as it has been suggested that this is the best measure of pentamidine delivery to its site of action [11, 12]. The validity of this measurement, however, depends on the unsubstantiated assumptions that the fate of the ^{99m}Tc HSA marker mirrors that of pentamidine 24 h after inhalation, and that mucociliary clearance is normal before and after *Pneumocystis carinii* infection in patients with AIDS [19]. It is also clear from the results that the information obtained from measurement of alveolar and peripheral deposition is similar, and it appears that there is no advantage obtained by making the more complex and time consuming measures of alveolar deposition.

Objective assessment of local side effects is always difficult, and the use of visual analogue scales can be criticised. We believe that the method used was adequate because the local side effect scores mirrored the particle size outputs of the nebulisers and the deposition of pentamidine in the upper respiratory tract which would be predicted to cause these unpleasant sensations. On the basis of these scores Respirgard II, Centimist, Samsonic, the modified System 22 Mizer, and Mizer/Optimist 2

were well tolerated, whereas the unmodified System 22 Mizer, Fisoneb and Pentasonic (Portasonic) caused more severe local side effects. These nebulisers also tended to produce larger reductions in lung function. These local side effects may be related to the acidic and hypotonic pentamidine solution, and might be reduced by the use of a suitable buffered isotonic preparation.

Our results show that Respirgard II produced a pulmonary deposition of 6.1 mgs, of which 75% was located distal to the mucociliary apparatus. This represents a deposition efficiency (lung dose/nebuliser dose) of 2.0%. This is consistent with our own previous estimates of 2.3–2.9% using pentamidine doses of 50–300 mg [8, 20], and, allowing for differences in methodology, with the values of 2.8–5.4% reported by others [21, 22]. The results of LEOUNG *et al.* [6] show this is an effective lung dose for prophylaxis when given once monthly. Other nebulisers which produced similar pulmonary deposition were Centimist, Mizer/Separator, Mizer/Optimist 2, Pentasonic (Portasonic), and Fisoneb. Of these, Pentasonic (Portasonic) and Fisoneb were associated with more larger local side effect scores, and Samsonic produced significantly less deposition than Respirgard II. Thus these 3 nebulisers cannot be recommended for pentamidine administration when used with this 300 mg dose and under these conditions. There is good clinical evidence, however, that use of Fisoneb and 60 mg pentamidine administered twice monthly gives effective prophylaxis [17]. The deposition efficiency of this dose may be improved because it is better tolerated: in one study deposition efficiency of pentamidine 60 mg was 5 times larger with Fisoneb than with Respirgard II [22].

In this study the unmodified System 22 Mizer produced over twice the pulmonary deposition associated with Respirgard II, and this was the case for total, peripheral, and alveolar deposition. These results, together with those reported previously [8] suggest that a dose of 150 mg pentamidine administered using this nebuliser would result in at least equivalent deposition in the lung to that produced by Respirgard II and a 300 mg pentamidine dose, and thus would be effective for prophylaxis. Only a randomized clinical trial would prove this hypothesis.

It is worthwhile considering deposition of aerosol in the upper part of the lung, as this is a common site for disease recurrence [23, 24]. With all the nebulisers, deposition here was less than that observed in the lower part of the lung. Inhalation of aerosol in the supine position has been shown to increase deposition of aerosol in the upper lung [20, 25], but to date there is no clinical evidence that this reduces the rate of disease recurrence.

It is important to prevent the escape of pentamidine aerosol into the environment to minimize possible side effects in health care workers involved in administering the therapy [26]. Respirgard II and Samsonic are supplied with suitable filters, and filters can be obtained separately for the modified and unmodified System 22 Mizer. Fisoneb and Pentasonic (Portasonic) were not supplied with appropriate filters at the time of this study and we had to make modifications to the inhalation apparatus and the method of inhalation to prevent aerosol escape. These modifications may have affected the

results of the study but we regard them as essential, not only for research studies using radioactive aerosol, but also for routine clinical pentamidine administration. The Centimist produces particular problems with environmental contamination as it has 4 entrainment ports in the storage chamber which allow some escape of aerosol.

The results of this study highlight the large differences in the performance of different nebulisers, with pulmonary deposition varying by up to 4 times. It is an anachronism that while the systemic bioavailability and efficacy of new oral drug formulations is closely monitored, there are no mechanisms to prevent the promotion of nebulisers which are associated with inadequate drug delivery or unacceptable side effects. The results of this study suggest that an adequate lung dose for effective prophylaxis can be achieved by Centimist, Fisoneb, and System 22 Mizer modified by the addition of various particle impingers, as well as by Respirgard II, using a nebuliser dose of 300 mg pentamidine once monthly, but Respirgard II is either better tolerated or produces less environmental contamination. Alternatively System 22 Mizer can be used with a reduced pentamidine dose. If the pentamidine in a 300 mg vial could be split between two patients, or if a 150 mg vial was produced, this would allow financial saving. Alternative equipment proposed for pentamidine administration should not be adopted unless the pulmonary deposition of pentamidine produced by that equipment is known, or there is adequate clinical proof of its efficacy.

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Quel aéroliseur pour inhaler la pentamidine? Une comparaison des dépôts pulmonaires par huit nébuliseurs. SHL. Thomas, M.J. O'Doherty, C.J. Page, T.O. Nunan, N.T. Bateman.

RÉSUMÉ: Une dose de 300 mg de pentamidine a été aérolisée dans une solution de 5 ou 6 ml a été administrée par huit systèmes de nébulisation différents à 12 patients atteints du SIDA. Les dépôts pulmonaires, extra-pulmonaires (gastriques et oro-pharyngés) et alvéolaires de pentamidine, ont été mesurés au moyen d'une gamma caméra grâce à l'emploi d'albumine sérique humaine marquée au ^{99m}Tc comme marqueur indirect de la pentamidine. Les effets secondaires (échelles visuelles analogiques) et les modifications de la fonction pulmonaire associées à chaque traitement, ont été quantifiés également. Le dépôt a été terminé plus rapidement avec les nébuliseurs ultrasoniques qu'avec les nébuliseurs à jet. Les dépôts pulmonaires totaux moyens ($\text{mg} \pm \text{SEM}$) furent les suivants: Respirgard II - 6.1 ± 0.5 , Centimist - 7.3 ± 1.0 , System 22 Mizer - 14.3 ± 2.1 , System 22 Mizer avec séparateur de particules - 4.5 ± 0.4 , System 22 Mizer avec Optimist 2 - 6.3 ± 0.9 , Fisoneb - 6.0 ± 1.2 , Pentasonic (Portasonic) - 4.6 ± 0.9 , et Samsonic - 2.9 ± 0.4 . Les différences entre les nébuliseurs, pour le dépôt alvéolaire, ont reflété les mêmes modalités. Les scores d'effets secondaires furent les plus élevés avec System 22 Mizer, Pentasonic (Portasonic), et Fisoneb, qui provoquaient également les dépôts oro-pharyngés et gastriques les plus importants. C'est avec System 22 Mizer que furent observées les réductions les plus importantes de la fonction pulmonaire.

Une dose de 300 mg pentamidine nébulisée par Respirgard II s'avère une prophylaxie efficace pour la pneumonie à *Pneumocystis carinii* lorsqu'on l'administre une fois par mois. Nos résultats montrent que des dépôts pulmonaires équivalents peuvent être obtenus au moyen d'autres nébuliseurs. System 22 Mizer donne un dépôt plus de 2 fois supérieur à celui du Respirgard II, et l'utilisation de doses de 150 mg de pentamidine est susceptible d'obtenir au niveau pulmonaire un dosage adéquat pour la prophylaxie. Ce nébuliseur, toutefois, entraîne des effets secondaires plus marqués.

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