Inhaled and Inspiratory Pattern Driven Nebulizers

In Vitro and In Vivo Comparison of Two Nebulizers Used for Inhaled Pentamidine Delivery

**Comparación en vitro e in vivo de dos nebulizadores utilizados para administrar pentamidina inhalada**

**Dear Editor,**

Pneumocystis jirovecii pneumonia (PJP) represents a significant cause of morbidity and mortality in immunocompromised patients.1,2 Pentamidine, used in secondary prevention of PJP, is administered via inhalation and requires a specific nebulizer.3,4 In the recent ERS/ISAM Task Force Consensus Statement, the RespirgardII® (Vital Signs) was considered as the reference nebulizer to deliver pentamidine.5 Nebulizers with comparable properties are required because RespirgardII® is no longer available since its recent withdrawal from the market in some countries.3 Most of the nebulizers compared previously to the RespirgardII were ultrasonic nebulizers.6 In this study, we compared a jet nebulizer (ISO-NEB®; Teleflex) to RespirgardII® for pentamidine delivery. Both nebulizers possess one-way valves on the inspiratory and on the expiratory way and an expiratory filter as recommended.3,4 Both were driven by a similar air flow (8 L/min) and deliver particles with similar size (MMAD: 1–2 μm).3,7,8 In vitro, nebulizers were connected to a dual chamber lung model (5600i Dual Adult Test Lung®, Michigan Instrument Inc.) driven by a ventilator (SERVO-1®; Maquet) in volume-controlled mode simulating an adult breathing pattern (Vt = 500 mL; RF = 15 breaths/min; I/E ratio = 1:2; no end-inspiratory pause) (Fig. 1). Artificial lung compliance and resistance were set to 70 mL/cmH2O and 5 cmH2O, respectively. Nebulizations of a pentamidine solution (300 mg/6 mL sterile water) were performed in triplicate for each model in accordance with manufacturer’s and guidelines recommendations until one minute after the appearance of the sputtering point.1,2,7,9 Inhaled dose, expressed in percentage of the nominal dose (ND), corresponding to the nebulized doses deposited on the filter interposed between nebulizer and lung model (weighed before the nebulization and after drying for 24 h) multiplied by the relative mass of pentamidine. The residual volume was also quantified.

In the in vivo part, after ethical approval (2013/27/JUI/375) and registration of the trial (NCT02277808), five non-smoker healthy male volunteers were recruited and signed a written informed consent. Each subject performed a spirometry according to the ATS/ERS guidelines.10 This was a randomized cross-over study based on CONSORT statement for clinical trials. Nebulizations of amikacin sulfate (Amukin®, Bristol-Myers Squibb) dissolved in 4 mL of normal saline (125 mg/mL) were made during 10 min with both devices. During nebulization, tidal volume (Vt; L), respiratory frequency (RF; min−1) and minute ventilation (VE; L/min−1) were monitored by inductance plethysmography (Respitraces®, Ambulatory Monitoring Inc.). Participants were requested (1) to empty their bladder before nebulization, (2) to inhale spontaneously through the mouthpiece with a nose clip in a sitting position, (3) to collect their urine for 24 h following nebulization and (4) to observe a wash-out period of one week between both nebulizations. Then comparison was performed by sampling the daily urinary excretion of nebulized amikacin following the technique previously described by Dequin et al.11 and analyzed by High Performance Liquid Chromatography. The total daily amount of amikacin excreted in the urine (Cu max) was calculated from cumulating amikacin amount measured at each micturition (Cu) and represents the lung dose. The elimination constant (Ke) was calculated from the fitted curve of the cumulated amount of amikacin excreted in the urine plotted versus the time. The equation is Cu = Cu max(1 − e−Keτ).

Inhaled dose was similar between devices, 28.7% (22.7; 33.5) vs 29.3% of ND (26.3; 33.1) for ISO-NEB® and for RespirgardII®

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**Fig. 1.** Schematic diagram of experimental devices used in the in vitro study.
We a, The In 698 needed ototoxicity Bibliografía are be was in values with reference (2–6.74% RespirgardII both were used devices previously we though it was not validated for pentamidine. However previous studies validated this process for different drugs. In vivo, we used amikacin sulfate because pentamidine has not been previously considered as a valid pharmacological marker of pulmonary deposition.11,15 For a methodological consideration, we recruited only male subjects because it is easier for a man to collect his urine without loss and to prevent potential fetal risk ototoxicity in pregnant female subjects. Finally, we did not measure the particle sizes for both nebulizers, but according to previous studies and manufacturer’s data we can consider that they were similar (1–2 μm). It is important to notice that the two nebulizers are in the same price range. In conclusion, this in vitro and in vivo study demonstrated that ISO-NEB® and RespirgardI®II have similar properties in the conditions study. Further clinical studies are needed to confirm that ISO-NEB® and RespirgardI®II have a valuable alternative to the reference nebulizer recommended by guidelines for pentamidine delivery. Altogether these data suggest that the performance of both devices is similar in the conditions of this in vitro and in vivo study.

Bibliografía


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Myobacterium xenopi and squamous cell carcinoma of the lung

Estimado Director:

Las micobacterias no tuberculosas (MNT) o micobacterias atípicas son bacterias aerobias del genero Mycobacterium, de potencial patógeno conocido desde los años cincuenta. La pandemia del sida, el incremento progresivo de los estados de inmunosupresión y el perfeccionamiento de las técnicas microbiológicas, hacen que el aislamiento de estos microorganismos sea más común en nuestros días.

Mycobacterium xenopi (M. xenopi) es una MNT relacionada con el agua que se encuentra fundamentalmente en América del Norte, sudeste de Gran Bretaña y norte de Francia, y que se demostró por primera vez en pacientes inmunodeprimidos. El principal factor de riesgo para la enfermedad son las enfermedades pulmonares crónicas, en las que el microorganismo puede colonizar las vías