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Experimentation with inhaled bronchodilators and corticosteroids

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ABSTRACT

Background: Inhaled bronchodilators and corticosteroids have been used for decades with different production systems.
Materials and methods: The following jet-nebulizers: (a) Invacare, (b) Sunmist, (c) Maxineb and ultrasound nebulizers: (a) GIMA, (b) OMRON and (c) EASY NEB II were used as production systems. The jet-nebulizers were used with different residual cups and volume filling, while the ultrasound nebulizers with different volume fillings and face mask versus inlet.
Results: Inhalation and ultrasound process detect significant differences between the factors and interactions considered, but each technique follows a specific pattern of magnitude effect. Thus the inhaled mechanism ranks the factor effects in decreasing order: residual cup > drug > nebulizer > loading (2, 3, 4 ml) and also drug > residual cup > nebulizer (loading 8 ml). The ultrasound mechanism orders as follows: nebulizer > drug > loading. In fact, varying micro environmental conditions created during the performance of the devices in both processes alternate the magnitude of factor significance allowing for unique capacities.
Conclusions: PULMICORT, MAXINEB, design cup J and loading 6 ml are the best options for the inhaled process. Optimal combinations are provided by FLIXOTIDE and cup B and also by MAXINEB and cup J. The incorporation of large residual cups suggests one out of six drugs, the SUNMIST nebulizer and design D as the best choices. Ultrasound performance informs for other optimal conditions: ZYLOREN, MAXINEB, 4 ml load and MAXINEB × loading 4 ml.

1. Introduction

Inhaled therapies are used by several medical principals in the everyday clinical practice. The administration of aerosol bronchodilators and corticosteroids are used by several patients with asthma, chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis and patients in a situation with respiratory distress (Chang et al., 2012; Dekhuijzen et al., 2013; Mogayzel et al., 2013). Bronchodilators assist in the dilation of the airways which are narrowed, while the corticosteroids reduce and block the inflammatory cascade release locally. There are currently several production systems such as; jet-nebulizers and ultrasound nebulizers, and systems that rely on the respiratory performance of the patients (dry powder inhalers, metered dose inhales) (Laube et al., 2011). Each system of aerosol administration has its advantages and disadvantages and depending on the patients' underlying disease, respiratory performance the medical doctor has to decide which method is the most appropriate. Nebulizers do not need coordination between patient and administration for maximum drug deposition as in the case of metered dose inhalers (MTI), while in the case of dry powder inhalers (DPI) misuse might lead to blowing the drug into the device. Moreover; the defense mechanisms of the respiratory system such as; beating cilia, mucus, enzymes,

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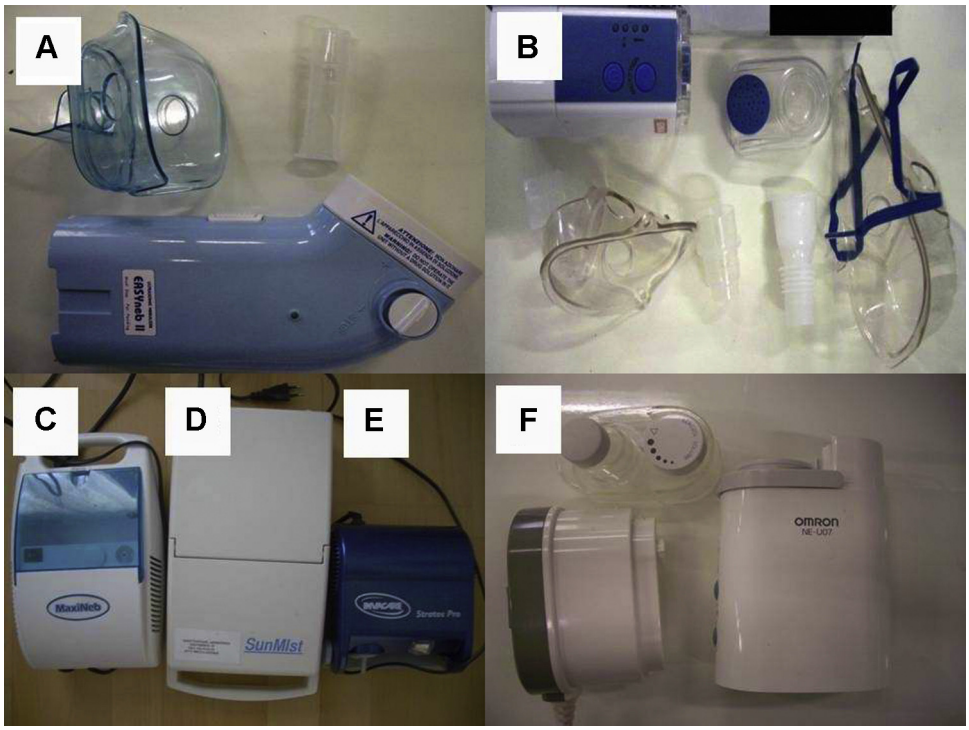

Fig. 1. Nebulizers jet (B–D), ultrasound (A, B and F).

local transporters/genes and macrophages play a crucial role in the deposition and absorption of the administered drugs (Zarogoulidis et al., 2013a). Humidity of the respiratory system is also responsible for expanding the droplets while moving from the upper respiratory system to the lower (Clay et al., 1983). Depending on the drug, the expansion differs between 25% and 50% of the produced size. It has been previously investigated that the optimal size for deep penetration, deposition and absorption into the lung parenchyma is the ≤5 μm mass median aerodynamic diameter (MMAD) (production size). The salts within a solution play also a crucial role in the expansion of the droplet size since a higher salt concentration results in a higher droplet expansion while the droplets travel from the upper to the lower respiratory tract (Bier et al., 2009). Regarding the production systems of jet-nebulizers the main factors affecting the droplet size are: (a) residual cup design, (b) drug (viscosity, electrostatic charge), (c) residual cup loading, (d) flow rate and (e) mouthpiece design (Clay et al., 1983; Kendrick et al., 1997; Mercer et al., 1969; Newman et al., 1985; Sterk et al., 1984; Zarogoulidis et al., 2013c,d). The time of nebulization is associated with the volume in the residual cup, the higher the volume the lower the nebulization time (Ferron et al., 1976). Therefore a technique that could be used is to refill the residual cup when volume of the solution reaches half of the initial included inside the residual cup. However; this method can only be applied once, since afterwards the concentration of the drug is minimized (Steckel and Eskandar, 2003). The ultrasound nebulizers have a different method of aerosol production (cavitation phenomenon (Lourenco and Cotromanes, 1982). The factors affecting the aerosol production can be summarized to: (a) temperature of the piezoelectric crystal, (b) drug (salts, viscosity), (c) addition of buffer, (d) time of nebulization (Dennis et al., 1990; Ferron et al., 1976; Niven et al., 1995; O'Callaghan and Barry, 1997; Steckel and Eskandar, 2003). The face mask and inlet has been also been observed to influence the droplet size production at least for inhaled insulin (Zarogoulidis et al., 2013d). It has been also observed that the addition of the gas CO_2 no more than 5–7% increases the tidal volume by 180% and reduces the respiratory frequency as a consequence the individual has deep slow breaths. However; this is not a common practice of aerosol administration. In the current experiment we evaluated residual cup designs, residual cup fillings, jet-nebulizers, ultrasound nebulizers, different bronchodilators, corticosteroids and the *z* potential of the aerosolized drugs.

2. Materials and methods

2.1. Aerosol production systems

2.1.1. Jet-nebulizers and residual cups

Three nebulizers were chosen from our department for the experiment: theMaxineb® (6 l/min and 35 psi), Sunmist® (5–7 l/min and 35 psi) and Invacare® (4–8 l/min and 36 psi) (Fig. 1). In total 7 residual cups were chosen for evaluation, four with a capacity of no more than 6 ml and two with a capacity no more than 10 ml. The designs for the large residual cups will be mentioned as A, D and E. The residual cups for the small residual cups will be mentioned as C, F, B and J (Figs. 2 and 3). The large residual cups were not used with a capacity of more than 8 ml as explained in Section 4.

2.1.2. Ultrasound nebulizers

Three new ultrasound nebulizers were chosen from the market based on their cost-effectiveness. The first was Omron® NE-U07, Tokyo, Japan. Compact and weight less than 350gm, includes 10 ml medication cup. Generates uniform micromillimetre-sized vapor particles. The second was a portable EASYneb® II, FLAEMNUOVA, Martino, Italy. With the following operating specifications; drug max capacity: 8 ml, Frequency: 2.4 MHz, Nebulization capacity (adjustable) 0–0.7 ml/min approximately (tests performed with saline 0.9%), Particle size: 2.13 μm (MMAD), sound level at 10 cm: 50 db (A), Operating temperature: min. 10 °C, max. 40 °C and air humidity: min. 10%, max. 95% RH. The third was a portable GIMA, Gessate, Italy (Choice Smart Health Care Company Limited, Wan Chai, Hong Kong, No. G2061259328002) with the following operating specifications; particle size: 3–5 μm, frequency: 2.5 MHz,