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Internal mouthpiece designs as a future perspective for enhanced aerosol deposition. Comparative results for aerosol chemotherapy and aerosol antibiotics

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ABSTRACT

Background: In an effort to identify factors producing a finest mist from Jet-Nebulizers we designed 2 mouthpieces with 4 different internal designs and 1–3 compartments.
Materials and methods: Ten different drugs previous used with their "ideal" combination of jet-nebulizer, residual-cup and loading were used. For each drug the mass median aerodynamic diameter size had been established along with their "ideal" combination.
Results: For both mouthpiece, drug was the most important factor due the high *F*-values ($F_{large} = 251.7$, $p < 0.001$ and $F_{small} = 60.1$, $p < 0.001$) produced. The design affected the droplet size but only for large mouthpiece ($F_{large} = 5.99$, $p = 0.001$, $F_{small} = 1.72$, $p = 0.178$). Cross designs create the smallest droplets (2.271) so differing from the other designs whose mean droplets were greater and equal ranging between 2.39 and 2.447. The number of compartments in the two devices regarding the 10 drugs was found not statistically significant (*p*-values 0.768 and 0.532 respectively). Interaction effects between drugs and design were statistically significant for both devices ($F_{large} = 8.87$, $p < 0.001$, $F_{small} = 5.33$, $p < 0.001$).
Conclusion: Based on our experiment we conclude that further improvement of the drugs intended for aerosol production is needed. In addition, the mouthpiece design and size play an important role in further enhancing the fine mist production and therefore further experimentation is needed.

1. Introduction

Currently the main mode of administration for several therapies is the intravenous route. In the previous years an effort was made to explore alternative routes of administration in order to enhance the efficiency of therapy and to minimize adverse effects. As it has been observed with several drugs, the adverse effects are directly related to the concentration administered (Miura et al., 2013). In several diseases the target lesion is located to a site which is difficult to approach directly and administer the optimal treatment. Therefore intravenous administration is administered in almost every disease. However; higher concentrations have to be delivered in older to have the desired result. In addition, the discomfort and adverse effects from the intravenous administration is another factor reducing the quality of life of patients (Baron et al.,

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2013; Wynne et al., 2013). The inhaled insulin was one of the first examples where a systematic therapy was redesigned to be administered as aerosol (Zarogoulidis et al., 2011). Inhaled antibiotics followed for patients with cystic fibrosis and patients admitted in the intensive care unit (Geller et al., 2007). Currently experimentation for lung cancer treatment is ongoing as local treatment in the form of intratumoral administration (endobronchial lesions) (Hohenforst-Schmidt et al., 2013), aerosol chemotherapy administration (Zarogoulidis et al., 2012a; Zarogoulidis et al., 2012b) and inhaled gene therapy (Zarogouldis et al., 2012; Zarogoulidis et al., 2013a; Zarogoulidis et al., 2012c). The safety of these novel treatment modalities is under investigation and currently several aerosol production systems are being developed (Darwiche et al., 2013; Zarogoulidis et al., 2013b; Zarogoulidis et al., 2013d). The main concept is to produce treatment administration modalities that are both effective and safe. In our previous work we divided the aerosol production methodology in two clusters: (i) the production system and (ii) the delivery system. We included in the production system the following parameters: (a) jet-nebulizer, (b) residual-cup design, (c) loading of residual-cup and (d) drug. We investigated the interaction of these four parameters between them to identify in what degree one affected the other. We identified for five chemotherapy drugs and five antibiotic drugs the "ideal" combination of these parameters producing the smallest droplets (mass median aerodynamic diameter < 5 μm). In our current work we investigated the "delivery system" which is the connection between the residual-cup and upper airways. There are two "delivery systems" that are used nowadays; (a) face mask and (b) mouthpiece. (Fig. 1.) Each one has its advantages and disadvantages which will be analyzed in the discussion section (Lin et al., 2007b; Sangwan et al., 2004). In specific eighteen different mouthpieces were designed in order to evaluate whether this part of the aerosol delivery process affects the mist production and hence the performance. It has been previous investigated that factors such as; turbulence, inlet size, air flow, mouthpiece and grid affect the production of the aerosol mist (Jiang et al., 2012). Inhaled insulin is an example again where different mouthpiece designs were investigated in an effort to enhance the aerosol production. Indeed the mouthpiece design was observed to be a key factor affecting the mist production at least for inhaled insulin (Boyd et al., 2004; Coates et al., 2007). The addition of a spacer has presented again favorable results when connected to a metered dose inhaler or jet-nebulizer production system (Silkstone et al., 2002). A third system identified to further influence the deposition of aerosol mist consists of the following geometrical factors; geometrical; mouth, oropharynx, larynx intra-thoracic airways up to six generations. The intra-thoracic airways however; is not a stable systems since the diameter changes due to underlying conditions (e.g. bronchoconstriction, excessive mucus production, viscosity of mucus) and diseases (e.g. chronic obstructive pulmonary disease, cystic fibrosis, asthma) (Lin et al., 2007a). The breathing pattern plays also an important role of aerosol deposition (Foust et al., 1991; Nikander et al., 2000). We will present our results and indicate future investigational directions towards the aerosol production methodology.

2. Materials and methods

2.1. Nebulizers

Based on our previous experiments we identified that for chemotherapy drugs (Cisplatin, Paclitaxel, Docetaxel, Gemcitabine and Carboplatin) the "ideal" combination producing the smallest droplets (mass median aerodynamic diameter) was the nebulizer Maxineb® (6 l/min and 35 psi), residual cup D with 8 ml loading (Zarogoulidis et al., 2013d). Regarding the antibiotics the "ideal" combination was for zobactam the residual cup C and G with 6 ml loading, for solvetan residual cup D with 8 ml loading and for maxipine, begalin, meronem residual cup C with 6 ml loading. There was no difference observed between the nebulisers (a) Sunmist®

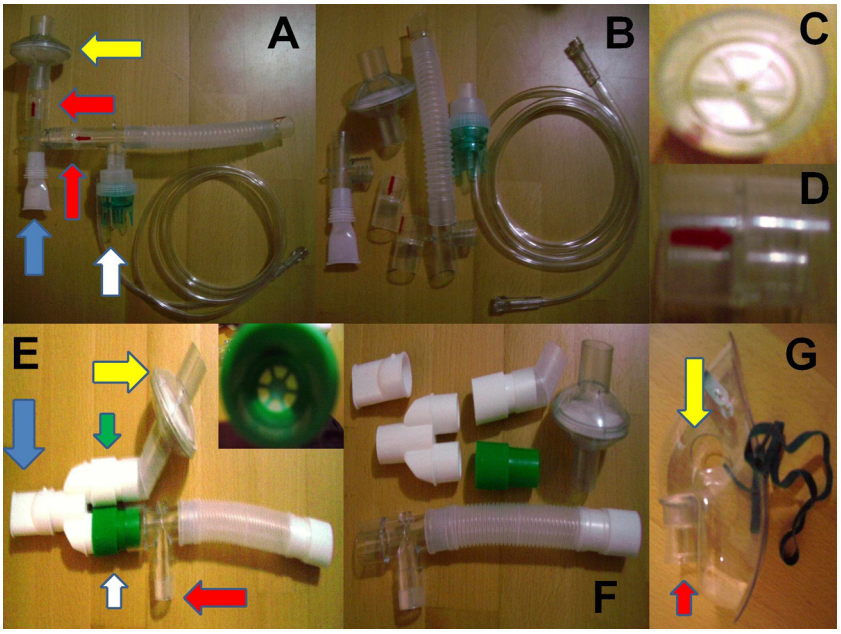

Fig. 1. (A) **ISO-NEB®** Filtered Nebulizer System, UP-DRAFT II-HUDSON RCI (TFX Medical Ltd., High Wycombe HP12 3ST U.K.), blue arrow indicates the mouthpiece, yellow arrow indicates the filter, white arrow indicates the residual cup and oxygen connection, red arrow indicates aerosol flow valve; (B) UP-DRAFT II-HUDSON RCI system parts, (C) valve inner design, (D) valve outer design, (E) Respiromed precision nebulizer special medication, Manufacturer: Int'Air Medical, F-01002 BOURG EN BRESSE, blue arrow indicates the mouthpiece, yellow arrow indicates the filter, white arrow indicates inspiratory breath activated valve (the inner structure of this valve is indicated on the upper right of the same figure), red arrow indicates the connection tip for the residual cup and the green arrow indicates the expiratory activated valve (the inner structure is the same as the expiratory valve), (F) Respiromed precision nebulizer special medication, Manufacturer: Int'Air Medical, F-01002 BOURG EN BRESSE parts, (G) facemask, red arrow indicates the connection tip of the residual cup and oxygen supply, yellow arrow indicates the face mask holes. (For interpretation of the references to color in the artwork, the reader is referred to the web version of the article.)