Technology in practice
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2014

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
CHAPTER 6

THE EFFECT OF A DISPOSABLE EXTENSION MOUTHPIECE ON THE AEROSOL FROM THE REDIHALER

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ABSTRACT

To allow the use of the salbutamol Redihaler by multiple patients as reliever medication during challenge tests in the clinic, a disposable extension mouthpiece with a one-way valve has been developed to prevent exhalation into the device. We investigated whether this mouthpiece affects the aerosol from the Redihaler in terms of its delivered dose and particle size distribution. Single shot impinger measurements and cascade impaction analyses were performed at three different flow rates: 30, 60, and 90 L/min. We found that the extension mouthpiece reduces the delivered dose by about 85% at 60–90 L/min and by 94% at 30 L/min, leading to the conclusion that 30 L/min is insufficient to open the mouthpiece’s valve completely. Furthermore, and as expected, the external piece selectively retains the larger particles from the aerosol, mainly those larger than 3 µm. Although the delivered dose from the Redihaler is greatly reduced by the disposable mouthpiece, comparable results can be found when a standard pressurised metered dose inhaler is used with a valved holding chamber. Therefore, in spite of the high losses, we consider the Redihaler with disposable extension mouthpiece suitable as alternative to the standard reliever medication (pMDI with a VHC), provided that the patient is instructed to inhale moderately forceful to allow proper opening of the valve in the mouthpiece.
INTRODUCTION

Bronchial challenge tests are widely used for the assessment of bronchial hyperresponsiveness and diagnosis of asthma. Since it is the actual aim of a bronchial challenge test to induce bronchoconstriction, safety is a very important aspect of the test. In order to counteract the bronchoconstriction when necessary (or when the test is completed), reliever medication should be readily available (35). Most often, the bronchodilator salbutamol is given to relieve the mild constriction that usually results from the challenge test.

For the salbutamol administration, a pressurised metered dose inhaler (pMDI) combined with a valved holding chamber (VHC) is generally used, which is equipped with a disposable mouthpiece to allow use of the same inhaler by multiple patients. Standard pMDIs are actuated by pressing down the canister. Upon actuation, the salbutamol dose is fired into the VHC, from which it can be inhaled in multiple breaths by the patient.

In contrast to standard pMDIs, the Redihaler pMDI is breath-actuated, i.e. the dose is fired upon inhalation through the pMDI by the patient. This feature may significantly increase both the treatment’s efficacy and convenience for use at home, since good actuation-inhalation coordination or the use of a VHC is no longer necessary. For use in the clinic, a disposable patient interface is required, to which end the manufacturer of the Redihaler has developed a disposable mouthpiece. Although in everyday language referred to as a ‘filter mouthpiece’ by the supplier, this extension part actually contains a one-way valve and not a filter. The valve is meant to prevent breathing into the Redihaler, which would render it unsuitable for use by other patients.

The aim of this study was to determine whether the Redihaler with the extension mouthpiece can be a suitable alternative to a standard pMDI with VHC for the delivery of reliever salbutamol in the clinic. We investigated how and to what extent the disposable extension piece affects the performance of the Redihaler by measuring the delivered dose and particle size distribution in the aerosol.
MATERIALS AND METHODS

Materials

Redihaler salbutamol 100 µm and disposable extension mouthpieces from TEVA Pharmaceuticals (Haarlem, The Netherlands) were used in the study. Salbutamol sulphate (*Ph. Eur*.), provided by DMV Fonterra Excipients (Goch, Germany), was used for preparing a calibration curve for UV analysis.

Single shot impinger measurements

The single shot impinger is a centrifugal wet particle collector that can be used to determine the dose that is emitted from inhalation devices. Delivered doses from the Redihaler with and without extension mouthpiece were determined at 30, 60, and 90 L/min. In accordance with the European Pharmacopoeia, 4 L of air was drawn through the device to collect one dose, for which 8, 4, and 2.7 s were required at 30, 60, and 90 L/min respectively. The single shot impinger was filled with 10 mL of water and ten doses were collected per measurement. Two series of measurements were conducted, consisting of one measurement without the extension mouthpiece and subsequently five measurements with the extension mouthpiece. Salbutamol deposition in the impinger was determined by UV spectroscopy at 225 nm.

Cascade impaction measurements

Cascade impaction measurements were performed with the Next Generation Impactor (NGI: Copley Scientific, UK). The NGI was cooled to approximately 5°C in the refrigerator prior to the measurements in accordance with the procedure recommended by Berg *et al.* for wet aerosols (264). This study also describes that the stage cups of the NGI can be used uncoated, since moist particles do not bounce off once they impact on the surface. The measurements were performed in duplicate at 30, 60, and 90 L/min. Equal to the single shot impinger measurements, 4 L of air was drawn through the device to collect each dose (at 8, 4, and 2.7 s measuring time respectively). Ten and twenty doses were collected per measurement without and with the extension mouthpiece respectively. Salbutamol deposition in the induction port and stage cups was determined by UV spectroscopy at 225 nm.
Data presentation and analysis

The delivered doses without extension mouthpiece are expressed as percentage of the label claim (100 µg). To allow for comparison of the effect of the extension mouthpiece on the delivered dose per flow rate, the delivered doses found with the extension mouthpiece were calculated as percentage of the delivered dose without mouthpiece measured at the beginning of the series. Unpaired two-sided Student’s t tests were performed to compare the delivered doses at the different flow rates. Probability values \( p < 0.05 \) were considered statistically significant.

Cumulative mass fractions deposited on the NGI stages were expressed as percentage of the label claim and plotted as function of the stage cut-off values corresponding with the flow rates adjusted. The relationships obtained were used to calculate subfractions <1, 1–3, and 3–5 µm respectively by linear interpolation.

RESULTS AND DISCUSSION

Delivered dose with and without extension mouthpiece

Although the inhaler was handled according to the instructions (vigorously shaken before use and discarding of the first doses), the delivered dose from the Redihaler without extension mouthpiece varied from 65 to 95% for the individual measurements. On average, we found delivered doses of 76, 70, and 95% at 30, 60, and 90 L/min, respectively, which suggests that there is no clear relationship between flow rate and delivered dose. However, there appeared to be an inverse relation between the delivered dose and the number of doses left in the inhaler, but this was not systematically investigated in this study.

Figure 6-1 shows the delivered dose from the Redihaler when the extension mouthpiece is used as percentage of the delivered dose without mouthpiece. A strong reduction was found at all flow rates, which was visually verified by deposition of powder on the inside of the extension mouthpiece. The reduction was most pronounced at 30 L/min, at which only 6% of the delivered dose relative to the dose without extension piece was recovered. This recovery was significantly lower than those at 60 and 90 L/min \( p < 0.0001 \). Between the two highest flow rates, no significant difference was found due to the large variation in the results \( p = 0.069 \).
The lower delivered dose found at a flow rate of 30 L/min can be attributed to the design of the extension mouthpiece. The valve within the mouthpiece appears to require a certain minimal airflow rate to open sufficiently wide for aerosol passage. A flow rate of 30 L/min does not suffice in this respect. Since no difference in delivered dose was found between 60 and 90 L/min, the threshold flow rate for complete opening the valve completely is expected to be anywhere between 30 and 60 L/min, but even after complete opening a substantial portion of the delivered dose is retained in the extension piece.

**Aerodynamic size distribution of the aerosol**

Figure 6-2 shows the fine particle fractions < 5 μm (FPF) of the aerosols with and without extension divided into three subclasses: < 1 μm, 1–3 μm, and 3–5 μm. At all flow rates, the diminishing effect of the extension mouthpiece on the FPF is apparent. Without extension mouthpiece, FPFs were 45, 48, and 37% of the label claim at 30, 60, and 90 L/min respectively. Comparing these values to the delivered doses found with the impinger, it can be seen that maximally 50% of the delivered dose is within the desired size range for good lung deposition. Remarkable is the lower fraction deposited at 90 L/min using the NGI compared to the impinger measurements. A reason for this might be that the higher airflow rate led to more turbulence in the NGI, thereby resulting in reduced deposition on the stages (265).
Disposable extension mouthpiece for the Redihaler

The FPFs with extension mouthpiece were 7, 10, and 13% of the label claim at 30, 60, and 90 L/min respectively. These values are comparable to the delivered doses found with the impinger. Additionally, Figure 6-2 shows that the extension piece selectively retains the largest particles. This finding can also be explained by the design of the extension piece. The particles emitted from the inhaler have to follow the change in airflow direction when they pass through the valve. The larger the particles are, the larger is their inertia, and the more likely they impact on the valve.

**Implications of using the extension mouthpiece**

We have shown that using the extension mouthpiece greatly reduces the dose that is delivered by the Redihaler. Especially at a flow rate of 30 L/min, only a very limited fraction of the aerosol was delivered from the mouthpiece. The Redihaler requires a flow rate of 20 L/min to fire its dose and the manufacturer of the Redihaler advises to inhale slowly through the device (266). When operated without extension mouthpiece, this advice should be heeded, since the higher the flow rate is, the more deposition occurs in the mouth and throat region. However, when the extension mouthpiece is used, inhaling with such low flow rates leads to insufficient opening of the valve, and hence, to insufficient release of the aerosol.

In addition, the disposable mouthpiece retains the aerosol selectively as only a small

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**Figure 6-2.** The fine particle fractions of the aerosols from the Redihaler with and without extension mouthpiece, expressed as percentage of the label claim (100 µg).
fraction larger than 3 µm was found to pass through the valve. Blocking the particles larger than 5 µm can be considered a useful feature of the extension mouthpiece, since these particles would otherwise deposit mainly in the mouth and throat and are therefore not desired. In contrast, the fraction 3–5 µm is highly wanted because this fraction is mainly deposited in the conducting airways, where constriction of the smooth muscle tissue is the main cause for the bronchoconstriction during a bronchial challenge test. Retaining this fraction may thus render the Redihaler less effective in counteracting breathlessness after challenge.

It should be noted that the Redihaler in combination with the extension mouthpiece is offered as an alternative to a standard pMDI in combination with a VHC. Hence, for its effectiveness it should be compared to this combination rather than to a pMDI alone. In terms of clinical effectiveness, no difference was found between four times 100 µg salbutamol administered by the combination of Redihaler and extension mouthpiece or Ventolin and Nebuhaler with a disposable valve (267). The comparable response to the two treatments may on the one hand be the result of the abundant dose of 400 µg, of which a sufficiently large fraction within the desired size range remains for deposition in the target area for patients to recover to baseline. On the other hand, VHCs are also known to retain a significant part of the aerosol, which – depending on the material of which the VHC is made and the environmental conditions – can become as high as 90–95% too (268,269).

**CONCLUSION**

Based on the combined results of this *in vitro* characterisation study with the clinical response data of Ruberg et al. (267), the salbutamol Redihaler (100 µg) with extension mouthpiece appears to be an suitable alternative to the standard rescue treatment after bronchial challenge, but only if the patient is instructed to inhale moderately forceful to allow complete opening of the valve.
Disposable extension mouthpiece for the Redihaler