Effect of an inhalation chamber without inspiratory valve and facemask for neonates use on drug delivery.

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Summary

The aim of this study was to evaluate *in vitro* aerosol delivery from a pressurized metered dose inhaler (pMDI) and inhalation chamber without inspiratory valve for neonatal patients compared with classic valved holding chambers (VHCs). The effect of mask holding duration to the model face on drug delivery was also investigated and measurements were performed with different numbers of breathing cycles after each pMDI dose release. Emitted drug mass was measured using a breathing simulator and aerodynamic particle size distribution (APSD) was determined with an *in Vitro in Vivo* Correlation (IVIVC) model from data collected with a cascade impactor at a constant flow of 15L/min. For both sets of measurements, the tidal breathing pattern of a neonatal patient was recreated by a breathing simulator. Inhalation chambers with facemasks were applied on an infant face model with a 0.8 kg force. Salbutamol sulfate, fluticasone propionate and beclomethasone dipropionate, were administered in separate experiments through the inhalation chambers. The aerosol dose delivered with the inhalation chamber without inspiratory valve was observed to be about 50% higher than the aerosol dose delivered with the classic valved holding chamber. The delivered drug dose increased with the number of breathing cycles after each pMDI dose release up to 14 cycles, corresponding to 16.2 seconds mask holding duration. Using an inhalation chamber without inspiratory valve increased the delivered drug dose and the facemask holding duration after each pMDI actuation has an impact on drug delivery.

Key Message

Removing the inspiratory valve of an inhalation chamber increases both *in vitro* delivered drug with a pMDI and fine particle dose (< 5 µm aerodynamic diameter) deposited to a filter distal to a neonatal model.

Introduction

Neonates have very low tidal volume, approximately 25mL, which is much smaller than the dead space of commercialized valved holding chambers with facemasks, between 43mL and 150mL [1]. This relationship could explain the inefficiency of inhaled treatments and the very low inhaled drug dose deposited reported for neonates when using a pMDI with a valved holding chamber [2]. One way to eliminate the dead space is to remove the inspiratory valve. A previous clinical study already suggested that using a spacer without inspiratory valve was more efficient to treat infants [3].

Another factor that could affect drug delivery when using pMDI and inhalation chambers for neonates is the cooperation of the patient. A decrease of drug delivered to the lungs was reported in crying children compared to quiet children [4]. Applying a mask on a baby's face during few seconds could result in the baby's stress and crying and reduce drug deposition to the lungs.

The aim of this study was to evaluate the *in vitro* performance of an inhalation chamber without inspiratory valve to be used with a neonatal model and compared to the *in vitro* performance of a classic valved holding chamber with different drugs used to treat neonates.

The effect of the number of breathing cycles after each pMDI dose release was also evaluated to determine how long it might be necessary to apply the inhalation mask on the baby's face after drug administration.

Materials and Methods

1) Emitted mass

A breathing simulator (BRS2000, Copley Scientific Ltd) was used to create the breathing pattern of neonates. In separate tests (n = 3 replicates), the pMDI was actuated (a) during the inspiration phase and (b) during the expiration phase to reflect coordinated and uncoordinated use respectively. A hydrophobic filter (Copley Scientific Ltd) was placed between an infant face model (Copley Scientific) and the breathing simulator to collect the drug that would likely be inhaled by a neonate (Figure 1). In each test, the facemask was applied to the face model with a 0.8 kg force. The first set of measurements was performed with the breathing simulator operating continuously between the actuations of the pMDI of salbutamol (Ventoline®, 100µg/dose, GSK). Subsequently, in separate tests the number of cycles studied between two actuations of beclomethasone dipropionate (QVAR Spray, 100 µg/dose, Teva) and between the last actuation and stopping the breathing simulator (holding duration in parentheses) were increased from 2 (2.6 seconds), to 4 (5.2 seconds), 6 (7.7 seconds), 8 (10.3 seconds), 10 (12.8 seconds), 14 (16.2 seconds) and 40 (51.2 seconds). In total, five salbutamol and five beclomethasone dipropionate doses were actuated into the inhalation chambers with 1

minute interval between individual actuations in order to have a sufficient amount of medication on the filter permitting an UV quantification.

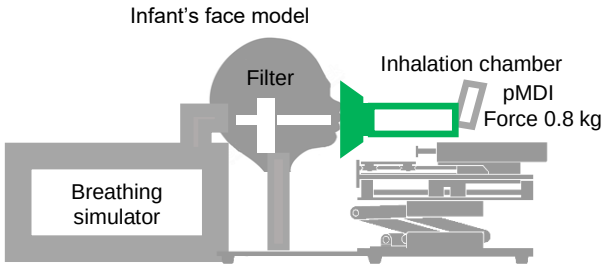

Figure 1 - Schematic drawing of the bench model for emitted mass.

2) Aerodynamic Particle size distribution (APSD)

APSD was measured during simulated tidal breathing using the experimental set-up (n = 3 replicate measurements) shown in Figure 2. A USP induction port (Copley Scientific Ltd.) was connected to the breathing simulator. A Next Generation cascade Impactor (NGI, Copley Scientific Ltd.) sampled the emitted aerosol by means of a T piece (mixing Inlet, Copley Scientific Ltd.). A constant flow rate of 15L/min through the NGI cascade Impactor was balanced with a pressurized dried air source of 15 L/min (with a relative humidity less than 10%) resulting in simulated tidal breathing through the VHC and constant air flow through the NGI. The inhalation chambers with facemask were again applied to an infant's face model (Copley Scientific) with a 0.8 kg force. Measurements were performed with the breathing simulator running continuously between the actuations of the pMDI. In total, ten actuations of fluticasone (Flixotide®, 125 µg/dose, GSK) were actuated during the expiratory phase with a 1 minute interval between individual actuations. The distribution of fluticasone through the different stages of the NGI was used to determine the APSD, the total mass of fluticasone recovered within the impactor (Impactor Mass, IM), the Fine Particle Dose (<5 µm, $FPD_{5\mu m}$) and the particle Mass Median Aerodynamic Diameter (MMAD).

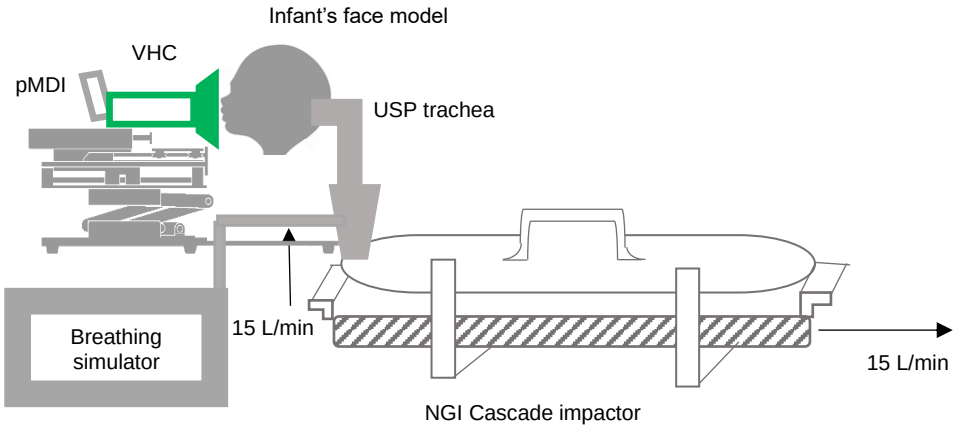

Figure 2 - Schematic drawing of the IVIVC bench model for APSD determination.

The drug deposited in all the components of the bench model was measured to evaluate the relative drug deposition on the filter compared to the total mass emitted from the inhaler. Deposited mass was quantified by UV spectrophotometry (Multiskan GO, ThermoFisher). Breathing parameters used were the representative tidal breathing pattern of a neonatal patient [5]: (tidal volume 24.7mL, frequency 52min^{-1}, inspiratory time/total time 0.47). Measurements were performed with the inhalation chamber TipsHaler® (Laboratoire OptimHal-ProtecSom) without inspiratory valve compared to the classic version of TipsHaler®. Results were expressed as percentage of the total mass recovered on the filter.

Results are expressed as means ± standard deviations. Statistical analyses were performed with RStudio (software version 1.2.5001). For each component, the percentage of drug deposited with the inhalation chamber without inspiratory valve was compared to that obtained with the VHC. A Shapiro test was performed to determine the

normality of the sample distribution. Variables normally distributed were subjected to a Student's t-test, and a Wilcoxon-Mann-Whitney test was applied for data not normally distributed. Two levels of significance were used: $p < 0.05$ *, $p < 0.01$ **.

Results and Discussion

1) Effect of removing the inspiratory valve on *in vitro* drug delivery

Figure 3 presents the percentage of the total mass of salbutamol deposited on the filter with TipsHaler® and TipsHaler® without inspiratory valve.

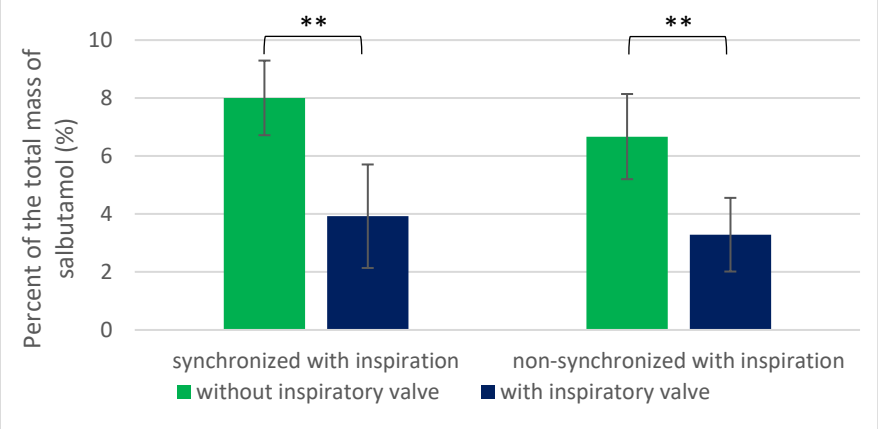

Figure 3 - Drug mass deposited on the filter when using TipsHaler® and TipsHaler® without inspiratory valve.

The low values of drug dose deposited on the filter with the valved holding chamber (3-4 % of the nominal dose) is consistent with drug deposition reported in previous studies to treat neonatal and infants patients [2][6].

The deposited drug mass when using TipsHaler® without inspiratory valve was significantly higher than when using the classic version of TipsHaler® independently of the synchronization or not of the actuations with the inspiratory phase.

Figure 4 shows the values of impactor total mass and fine particle total mass of fluticasone propionate obtained with the APSD measurements when using TipsHaler® without inspiratory valve and when using the classic valved holding chamber. Table 1 shows the MMAD obtained with the two inhalation chambers.

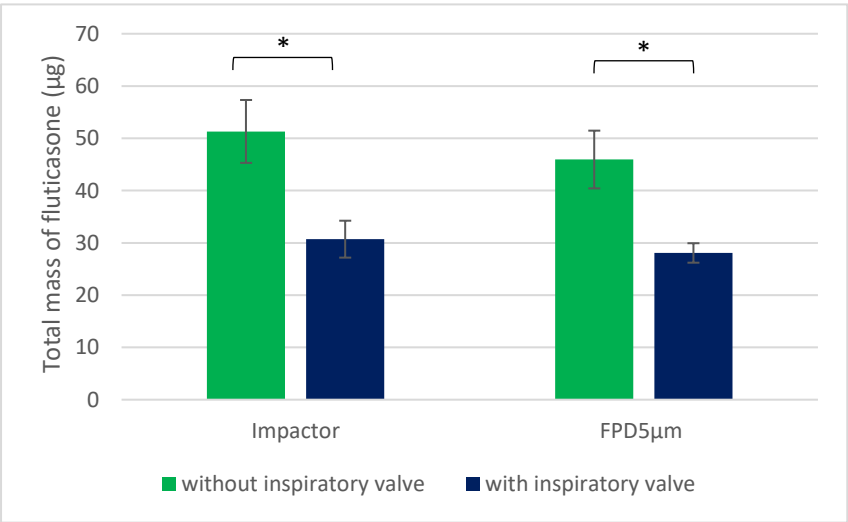

Figure 4 – Total drug mass deposited on the impactor and fine particle dose (lower than 5µm) with TipsHaler® without inspiratory valve and TipsHaler®.

Table 1 – MMAD obtained with TipsHaler® without inspiratory valve in comparison with TipsHaler® with its inspiratory valve.

	without inspiratory valve	with inspiratory valve
MMAD (µm)	2.32 ± 0.28	2.40 ± 0.21

The total mass of fluticasone collected in the NGI with the valved holding chamber is very low. This may be due to the dead volume, which includes the volume of the valved holding chamber, mask and USP throat. This dead volume is larger than the tidal volume, which should prevent drug from depositing in the impactor. It is supposed that the drug could deposit in the NGI due to the breathing pattern and the number of breathing cycles. Indeed, the inhalation profile has a higher amplitude than the exhalation profile, which could allow some drug particles to not be expelled and to enter the impactor during the next inhalation phase.

Both impactor mass and fine particle mass were significantly higher when using TipsHaler® without inspiratory valve in comparison with the classic version of TipsHaler®. MMADs were not statistically different when using TipsHaler® with or without the inspiratory valve.

2) Effect of mask holding duration on *in vitro* drug delivery

Figure 5 presents delivery of beclomethasone dipropionate obtained as a function of the number of breathing cycles after each pMDI dose release with the inhalation chamber without inspiratory valve.

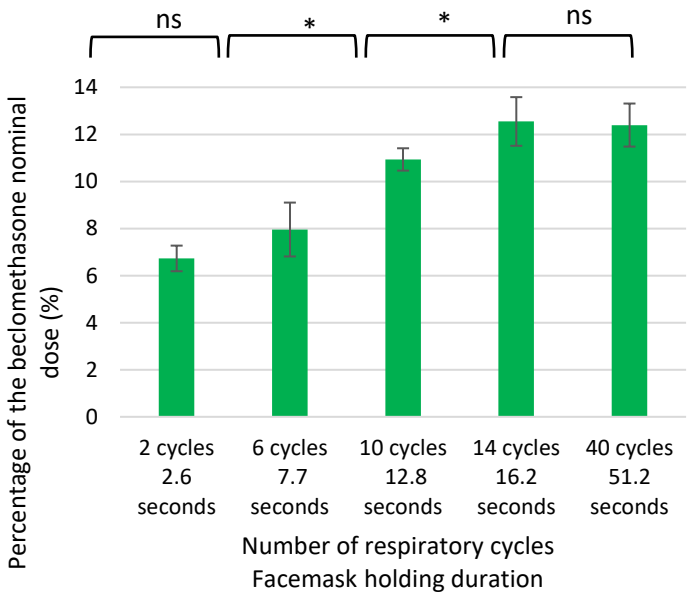

Figure 5 - Drug mass deposited on the filter using TipsHaler® without inspiratory valve as a function of the number of breathing cycles after pMDI actuation for different facemask holding durations

The delivered mass of beclomethasone dipropionate increased with the number of breathing cycles up to 14 cycles corresponding to 16.2 seconds holding duration. However, the mass deposited after 2 cycles was higher than 50% of the maximum dose deposited.

These *in vitro* results were obtained in ideal conditions. In the clinical situation, it could be interesting to consider the benefits of using a protocol involving administration of two drugs doses instead of one and applying the facemask for only 2.6 seconds twice instead of once for a16.2 second holding duration to avoid and reduce stress and crying of the baby.

Conclusions

These *in vitro* data offer new perspectives on how to treat neonates. The results obtained showed that drug deposition for neonates seemed to be affected by the dead space volume. Indeed, the inhalation chamber without inspiratory valve was associated with more drug mass-per-actuation deposited together with a higher fine particle mass. Pneumatic nebulizers are also associated with low drug dose deposited for neonates but are very

constraining [7]. Using a holding chamber without dead space volume with a pMDI could thus be an alternative to the use of a pneumatic nebulizer.

The effect of holding time of the facemask on the face model after a inhaler actuation on *in vitro* drug delivery was evaluated with a valved holding chamber (data not plotted) and with a device without inspiratory valve. The findings obtained raise a question: What is more beneficial for clinicians and patients, using two pMDI doses and holding the mask for 2.6 seconds twice or using one pMDI dose and holding the mask on the baby's face for a longer time (16.2 seconds), with the risk of reducing the drug dose deposited because of the baby's crying?

References

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