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The emitted dose of drug from a valved holding chamber using five pressurized metered dose inhalers

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Abstract

Background. The dose available at the mouth from a pressurised metered-dose inhaler (pMDI) cannot stay the same if it is used with a valved holding chamber (VHC). A different aerosol drug delivery system is created when the pMDI is used with the VHC and therefore the dose delivered to the patients is no longer that released from the pMDI alone, but the one emitted by the new system. This study aims to verify the emitted dose of five pMDI drugs when used with a VHC.
Methods. The emitted dose was expressed as the amount of drug within the respirable fraction available at the end of the VHC, i.e. the drug output (measured by high performance liquid chromatography) multiplied by the percentage of FDF determined using a laser diffraction analyser.
Results. the emitted doses were drastically reduced in comparison with the nominal doses (Beclomethasone from 250 to 90.5 µg, Budesonide from 200 to 100 µg, Ciclesonide from 160 to 102 µg Fluticasone from 250 to 116 µg, Salbutamol from 100 to 54 µg).
Conclusions. When pMDIs are employed with a VHC, the emitted dose drastically changes; it is more or less halved. In order to facilitate prescription by the physician, both the nominal and the emitted doses should be reported in the VHC package.
Keywords: emitted dose, FPF, FPD, nominal dose, pMDI, VHC.

Introduction

Drugs for the treatment of asthma and asthma-like symptoms are frequently delivered from a pressurized metered dose inhaler (pMDI) used alone or with a spacer device. It has been reported that the pMDI effect is spacer-device dependent. [1] A valved holding chamber (VHC) decreases ballistic drug deposition in the oropharynx reducing the total body dose by 75%, improves the lower respiratory tract drug delivery efficiency of small aerosol particles by 30-50%, increases the therapeutic ratio, and facilitates patient and task specific aerosol delivery,[2]
Aerosol therapy is a complex process dependent on aerosol drug delivery system (ADDS) performance and patients' features. In order to avoid errors, these variables should be studied separately. [3] In the case of pMDIs, ADDS performance can be expressed as the amount of drug contained in an actuation (nominal dose). It is known that a different ADDS is created when the pMDI is used with a VHC; the dose available at the mouth is no longer that released from the pMDI alone, but the one emitted by the new system. In this case, the delivered dose is the fine particle dose (FPD), an objective parameter by which to quantify the amount of drug within the respirable range available at the end of the pMDI-VHC system [4] and potentially capable of reaching the lower airways. This mechanical method has been suggested in order to standardize first-step aerosol therapy. [5] Many studies have evaluated the effect of different VHCs for the delivery of single drugs using sampling mechanical methods reflecting different patient techniques. [6-9] In fact, the emitted dose is calculated using mechanical filters that change the resistance of airflow rather then respecting the breathing pattern of the patients. Furthermore, the emitted doses of different drugs at the end of the pMDI-VHC is never reported in the "Summaries of Product characteristics" and "Patient information Leaflets" of any VHC.
The aim of this study was to verify this difference in the emitted dose by comparing the five most frequently used pMDI drugs when delivered without and with a VHC.

Materials and methods

The five pMDI drugs currently available on the market, namely Beclomethasone, Budesonide, Ciclesonide, Fluticasone and Salbutamol, were analyzed when used with a VHC (L'Espace, Air Liquide, Bovezzo Bs, Italy). This VHC with mouthpiece is declared

universally compatible with the pMDIs. It has a polycarbonate chamber, and silicone valves, masks and MDI inlet. The plastic used has very low electrostatic properties. The chamber volume is 220 cc and its dimensions are 6x6x15cm.

Puff concentration, excipients and the same drug available in solution form used for high performance liquid chromatography (HPLC) reference are reported in Table I. All pMDIs employed hydrofluoroalkane as the propellent and were therefore chlorofluorocarbon free.

Fine particle fraction (FPF): a laser diffraction analyzer (particle size distribution analyzer model 3603 produced by TSI and validated by Air Liquide Medical Systems compared to cascade impactor as requested by UNI EN 13544-1:2009) was used to determine the aerosol particle-size distribution, [10] i.e. the fraction of aerosol capable of entering and remaining in the lung was calculated. The particle-size distribution was used to calculate the respirable fraction as the fraction of the volume of aerosol contained in particles of 1 - 4.6 mm in diameter. [11]

Subjects. Five patients (4 males, 1 female, mean age 50.4 ± 11.7 years); with normal spirometric values (exclusion criteria: previous treatment with selected pMDI drugs), were invited to take their treatment in our laboratory three times consecutively. The concentration of drug residual assay in the VHC was determined immediately after treatment in duplicate by HPLC.

Sample collection. The patient was given the selected pMDI attached to the VHC and told to press the device and to inhale three times, consecutively. The chamber was then thoroughly washed with the elution mixture and brought to 20 mL.

HPLC analysis. The chromatography equipment consisted of a 2996 diode array detector and a 600 E Multisolvent Delivery system (Waters, Milford Massachusetts, USA) equipped with a 20 μL loop. The chromatographic system was controlled by the Empower Pro software (Waters). The column was a Geminy-NX, 4,6 x 250 mm, with 5 μm pore size and 110 Å particle size (Phenomenex, Torrance, USA) protected by a guard cartridge from the same package. Four drugs were assessed using a 10 min isocratic elution, with different percentages of methanol in water, and different flow rates, except that in the case of Salbutamol, where a gradient elution was applied, starting with a 50% of A and B, mantaining it for 4 min, then linearly increasing solvent B to 100% during the following 4 min.

A calibration curve was obtained for different amounts of commercial drugs in solution depending on the reported values of concentration, which were taken to be exact; in the case of Ciclesonide, no commercial solution was at hand, so a solution was prepared by puffing directly into a suitable amount of solvent. All samples were filtered through Waters HA 0.45 mm filters before injection.

Results

The elution conditions used in the HPLC analysis were derived in part from the paper of Steckel and Möller. [12] Owing to the fact that only one drug at a time had to be measured, the amount of each compound was easily determined using the same column, using different eluent composition and flow rate at the wavelength of maximum absorption, as reported in Table II.

Measured values were highly reproducible, obeying a linear law with a R^2 always higher then 0.998 and with a good limit of quantification (LOQ), namely of 1.1, 0.9, 1.6, 0.54, and 1.3 mg/L for Beclomethasone, Budesonide, Ciclesonide, Fluticasone and Salbutamol, respectively.

Table III shows the FPD available at the end of the VHC; this represents the emitted dose according to the formula described by Malone [4] and summarizes the comparison of the emitted dose of the drugs delivered by pMDI with or without the VHC.

Discussion

pMDI and VHC should be considered a single ADDS, since the emitted dose is no longer that released from the pMDI alone, but the one emitted by the new system.

Our data confirmed that, when pMDIs are employed with a VHC, the emitted dose changes; [13-17] it is more or less halved (36-74%). This shows that VHC characteristics interfere drastically with pMDI drug delivery, as already reported. [18] On the basis of this evidence, many patients probably do not use VHC-pMDI drugs properly and do not receive the optimal therapeutic dose. [19] EMA guidelines recommend that the development of a pMDI should always include testing of at least one specific spacer for use with a particular pMDI. [20] In fact, some pMDIs are licensed with a specific spacer. We agree that if a pMDI has been designed for use with a specific spacer it should always be used with this named spacing device. However, in this case both should be present in the same package to avoid misuse and this must also be reported in the product warnings: “these instructions are not necessarily valid when this pMDI is used with other spacers”. As an alternative, manufacturers could verify the compatibility between pMDI drugs and spacer use, determine the emitted doses of different drugs and report these data in the “Summaries of Product characteristics” and “Patient information Leaflets” of all VHC for all pMDIs in order to facilitate prescription by the physician.

As far as we know, ours is the first report to propose a simple method of testing the interference of a VHC on the emitted dose of all of the five most frequently used drugs respecting the breathing pattern of the patients rather than using mechanical filters that change the resistance of airflow. In this paper, the percentage of output in the respirable range was measured by a laser particle analyzer in continuous nebulization to the same point of abrupt drop in output. The calculation of the emitted dose proposed in this paper is not intended to be a simulated therapeutical dose as this would include patient variability, but it is nonetheless adequate to provide the information necessary for the Product Leaflet. In 2007,

Table I. Pressurized metered dose inhaler drugs currently available on the market (nominal dose in µg/puff , without spacer), excipients and reference solutions.

Drug	pMDI µg/puff	Excipients	Reference solution (mg/mL)
Beclomethasone	250	ethanol, glicerol	0.4
Budesonide	200	ethanol, oleic acid	0.25
Ciclesonide	160	ethanol	not available
Fluticasone	250	-	0.25
Salbutamol	100	ethanol, oleic acid	5

Table II. HPLC parameters applied to assay the amount of each drug.

Drug	Eluent		Method	V	λ max
	A	B	isocratic (A:B)	(mL/min)	(nm)
Beclomethasone	water	acetonitrile	40:60	1.2	239
Budesonide	water	methanol	20:80	1.5	244
Ciclesonide	water	acetonitrile	10:90	1	241.7
Fluticasone	water	acetonitrile	40:60	1.2	235.8
Salbutamol	water	methanol	Gradient	1	225

Table III. The Fine Particle Dose (FPD) available at the end of the spacer and the emitted dose of the drugs delivered by pMDI with or without the VHC (nominally released dose per actuation)

Drug	FPD ± SD (%)	Amount of drug ± SD (µg)	FPD	Emitted dose with VHC	Emitted dose without VHC	%
Beclomethasone	77 ± 6.5	117.5 ± 12.5	90.5	90.5	250	36.2
Budesonide	91 ± 8.3	110 ± 20	100	100	200	50.0
Ciclesonide	77 ± 4.7	133 ± 10	102	102	160	63.7
Fluticasone	91 ± 7.7	127 ± 32	116	116	250	46.4
Salbutamol	83 ± 8.1	65 ± 11	54	54	100	54.0

Abbreviation: SD = standard deviation

Mitchell et al. has already evidenced some improvements that might be added by manufacturers of VHC devices in order to avoid an inconsistent medication delivery, [21] however this lack we observed was not reported.

A limit of our study is that, for technical reasons, we were only able to study one VHC. It would be interesting to evaluate the other commonly used spacers (such as AeroChamber, InspirEase and Volumatic) to see how much of an effect each spacer has on the drug output from the different pMDI-VHC systems.

Conclusion

When pMDIs are employed with a VHC, the emitted dose is more or less halved. Multiple measurements from each pMDI-VHC system are encouraged with the reported method in order to

determine how uniform and reliable the delivery of drugs is from each pMDI-VHC system.

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