Available online on 15.11.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Nebulized Glycopyrronium and Formoterol, Budesonide Aerosol Aerodynamic Assessment with Vibrating Mesh and Compressor Air Nebulizer: Anderson Cascade Impactor Study

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ABSTRACT

Vibrating mesh nebulizers (VMN) demonstrate improved efficiency for delivery of inhaled aerosol solutions or suspensions as compared to compressor devices. The added advantages of compactness, portability and functioning as noise-free device makes them of incremental value in Home or Ambulatory settings while managing Severe Obstructive airway disease or delivery of maintenance medications in these cases. This further circumvents the need for multiple devices thereby further improving patient compliance and convenience while delivering acute or maintenance formulations including Glycopyrronium (GLY) and Formoterol (FRM)/Budesonide(BUD) nebulizing solution formulations. To further assess the clinical role and feasibility of FRM-BUD formulation delivery kinetics with or without GLY nebulizing solution through VMN and jet nebulizers for In- & outpatient settings, 2 comparative *in-vitro* lung deposition studies were carried out utilizing Anderson Cascade impactor at 30 L/min; with deposited drug estimated by HPLC. Post-hoc analyses with $p<0.05$ were considered statistically significant for intergroup differences on FRM/BUD and GLY delivered through VMN or Compressor devices. The calculated mean fine particle dose for FRM & BUD delivered by VMN or jet nebulizer showed no statistical difference. However the mean fine particle fraction for BUD delivered by VMN was significantly better compared to jet nebulizer. The Residual volume at 10 mins was significantly higher with jet nebulizer. The optimal Aerodynamic Particle Size Distribution (APSD) for GLY nebulizing solution admixture with FRM/BUD suspension delivered through VMN and Jet nebulizer offers a clinically relevant strategy for High risk COPD cases in Acute or Home settings.

Keywords: Anderson cascade impactor, Fine particle fraction, Fine particle dose, Glycopyrronium, Formoterol/Budesonide, Nebulizing formulation, Vibrating Mesh nebulizer

Article Info: Received 09 Aug 2019; Review Completed 03 Sep 2019; Accepted 23 Sep 2019; Available online 15 Nov 2019

Cite this article as:

Menon MD, Naik IV, Rajawat G, Nagarsenker MS, Krishnaprasad K, Nebulized Glycopyrronium and Formoterol, Budesonide Aerosol Aerodynamic Assessment with Vibrating Mesh and Compressor Air Nebulizer: Anderson Cascade Impactor Study, Journal of Drug Delivery and Therapeutics. 2019; 9(6):79-82 http://dx.doi.org/10.22270/jddt.v9i6.3465

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INTRODUCTION

India has growing burden of chronic respiratory diseases including Bronchial asthma, asthma-COPD overlap (ACO) and COPD that are an important contributor towards deaths and disability adjusted life years (DALYs).

The contribution of chronic respiratory diseases to the total DALYs in India increased from 4·5±0.4%in 1990 to 6·4±0.6%in 2016. Of the total DALYs due to chronic respiratory diseases in India, COPD and asthma account for 75·6% and 20·0% respectively[1].

Recent studies of peak inspiratory flow after recovery from an acute exacerbation found that 19%–52% of COPD patients had insufficient peak inspiratory flow for effective DPI use, and those patients were more likely to be older and have more severe disease[2]. In most of these cases (ie. GOLD D), the administration of ICS/LABA and LAMA remains a clinical challenge with the conventional devices with almost one-third of the post-discharge cases having low peak inspiratory flow rate (PIFR) of ≈30% l/min following a severe exacerbation. However in case of a differential diagnosis involving clinical symptomatology of ACO, baseline therapy of ICS/LABA with LAMA is again recommended[3]. In either of these cases, education, adherence and review of patient inhalation technique in the post-discharge phase remains critical for optimizing health outcomes especially with conventional devices.

A systematic review found that 45% of pMDI users had suboptimal hand-breath coordination for optimal drug delivery. Coordination limitations can be addressed by the

use of holding chambers or spacers; however, errors in handling, execution, and breath holding technique are still common[4,5].

The mainstay of treatment involves delivery of rescue and maintenance therapies through a compressor air (jet) nebuliser along with short course therapy with steroids and antibiotics. Compressor air nebulizers commonly used in hospitals require a compressor or pressurized gas source to operate, and tend to be inefficient, leaving up to 1.4mL of medication in the reservoir at end of dose. To overcome the limitations of compressor air nebulizers, several new nebulizer technologies, such as active vibrating mesh nebulizers (VMN), have been developed. The VMN is electronically operated, requiring no gas to generate aerosol, with greater efficiency associated with low residual drug volume at end of nebulization (< 0.1 mL)[6-8]. while delivering rescue or maintenance nebulizing solutions including ICS/LABA and/or anticholinergics.

Glycopyrronium and Formoterol/Budesonide nebulizing formulations have been available as Maintenance therapy for the management of obstructive airway diseases and related phenotypes including ACO[9]. Combination of these drug solutions or suspensions in the nebulizer for simultaneous nebulization remains a pertinent strategy in clinical practice[10]. However, little information is available on the compatibility of drugs when admixed for the effect on particle size distribution and aerosol output

To further assess the clinical role and feasibility of Formoterol/ Budesonide formulation delivery kinetics with and without combination with Glycopyrronium formulation through VMN and Compressor air nebulizers for In- & outpatient settings, two comparative *in vitro* lung deposition studies were carried out utilizing Anderson Cascade impactor

MATERIAL AND METHODS

The *in vitro* Lung deposition studies were carried out using Anderson Cascade impactor (ACI) at 30 L/min using Nebulizing formulations of Glycopyrronium (25 mcg/2 ml) and Formoterol/Budesonide (20 /500 mcg) provided by Glenmark Pharmaceuticals Ltd.

The ACI study was carried out for the assessment of the aerodynamic properties of the above mentioned products for nebulization using both the nebulizers, i.e. jet and the vibrating mesh types. Inspiratory flow rate of 30L/min was used as per manufacturer's specifications (Copley Scientific).ACI was assembled with glass fiber filter and stages (S-0, S1, S2, S3, S4, S5, S6, S7).

Formoterol/Budesonide smartule 20/500 mcg/ 2 ml for Study I and Formoterol/Budesonide smartule 20/500 mcg/ 2 ml & Glycopyrronium nebulizing solution 25mcg/ 2ml for Study II were opened and the contents placed in nebulizer medication chamber. For Compressor air nebulizer, the smartule content were diluted with distilled water. The length of the time interval for nebulization for each device was decided based on the time required for the delivery of volume of MilliQ water equivalent to the volume of contents of the smartule and the diluent for the corresponding nebulizer device, ensuring the sufficient amount of drug to be delivered in the ACI assembly for the purpose of quantification. Apparatus was dismantled and each stage and filter were carefully washed with suitable solvent (diluent-Methanol AR: MilliQ water in 60:40 ratio) and washings collected into a beaker (Volume of the solvent used: 25 ml for Device and induction port washings and 10 ml for remaining stages). Active substance at each stage (deposition) was determined by using developed reverse phase gradient HPLC method of analysis.

The recovered active substance deposition from each stage of the cascade impactor was processed in the CITDAS software provided by Copley Scientific Ltd. UK. The characteristics of the aerosol were determined and assessed using several parameters including fine particle fraction (FPF), MMAD, and fine particle dose (FPD). The definitions included FPF: Fraction of the aerosol that is in a size range with the potential of the fine particle (<5 μ) dose divided by the total delivered dose; MMAD: Diameter of drug particles at which 50% of particles by mass is larger and 50% are smaller; FPD is the quantity of drug with fine particle size and related to drug deposition in the lung,[4-6]

RESULTS

In vitro Lung deposition was characterized by FPD, FPF, MMAD, Nebulization time & Residual volume for Formoterol/Budesonide & Glycopyrronium nebulizing suspension delivered by VMN or Compressor air nebulizer in both the studies. (Tables 1, 2)

In Study I, the calculated mean FPD for Formoterol & Budesonide delivered by VMN or Compressor air nebulizer showed no statistical difference (p= 0.19 & p=0.15 respectively). Similarly, the mean FPF for Formoterol was again comparable in both the arms (p= NS) with incremental impact on Budesonide delivery by VMN that was significantly better compared to Compressor air nebulizer (p=0.04). The Residual volume at 10 mins was significantly higher with Compressor air nebulizer (0.5 ml).

Table 1: Study I, *in vitro* Lung deposition study results using ACI with VMN & Compressor air nebulizer for Formoterol/ Budesonide nebulizing suspension

Sr. no.	Parameter	Vibrating Mesh Nebulizer		Compressor Air Nebulizer	
		Formoterol	Budesonide	Formoterol	Budesonide
1	FPD	11.9±3.0*	183.2±63*	7.3±0.2	71.1±11.2
2	FPF	68.4±8.6*	62.2±5.03#	59.7±1.6	45.5±2.2
3	MMAD	3.7±0.5*	4.3±0.2#	4.5±0.1	5±0.1
4	Residual Volume	Negligible		0.5 ml	

*p=NS vs Compressor air nebulizer; #p<0.05 vs. Compressor air nebulizer.

FPD: Fine Particulate Dose (<5μ); FPF: Fine Particle Fraction (% Drug <5μ); MMAD: Median mass aerodynamic diameter

The second study (Study II) explored for the first time the clinical feasibility of Glycopyrronium solution admixture with Formoterol/Budesonide formulation assessing the APSD or delivery kinetics in real world outpatient settings of India. In case of formoterol Fumarate, glycopyrronium and budesonide there is no statistically significant difference observed in MMAD, FPD, and FPF between two nebulizer devices.

Table 2: Study II, *In vitro* Lung deposition study results using ACI with VMN & Compressor air nebulizer for Formoterol/ Budesonide nebulizing suspension in combination with Glycopyrronium nebulizing solution

S. N.	Parameter	Vibrating Mesh Nebulizer			Compressor Air Nebulizer		
		Formoterol	Budesonide	Glyco-pyrronium	Formoterol	Budesonide	Glyco-pyrronium
1	FPD	10.59 ± 4.08*	139.21 ± 67.58*	15.22 ± 7.34*	7.06 ± 2.52	116.14 ± 65.65	14.99 ± 9.03
2	FPF	48. 88 ± 6.74*	43.77 ± 13.16*	54.44 ± 10.26*	45.34 ± 14.12	42.94 ± 6.06	57.19 ± 14.37
3	MMAD	4.97 ± 0.67*	5.1 ± 0.75*	4.44 ± 1.06*	5.1 ± 0.66	5.2 ± 0.26	4.4 ± 1.22
4	Residual Volume	Negligible			0.12 ml		

*p=NS vs Compressor air nebulizer; #p<0.05 vs. Compressor air nebulizer

FPD: Fine Particulate Dose (<5µ); FPF: Fine Particle Fraction (% Drug <5µ); MMAD: Median mass aerodynamic diameter

DISCUSSION

This is the first study to assess the pharmacokinetic compatibility and delivery kinetics for Formoterol/ Budesonide with or without Glycopyrronium nebulizing formulations when admixed at the same time for delivery with Active vibrating mesh and compressor air nebulizer. The only publications till date by Akapo[11] and Kamin[12] suggest the likely compatibility of above formulations as admixture with no further evidence on the clinical impact or *in vitro* lung deposition or APSD assessments. These results have likely impact on the clinical role of Home nebulization for delivery of Rescue or Maintenance therapies particularly in High risk COPD cases while preventing 30-day readmission or 1-yr mortality that is quite common in such cases[13,14] due to varying reasons including nonadherence or suboptimal utilization of the conventional devices.

In this line Home nebulization with the conventional compressor air nebulizers are often considered cumbersome, bulky, noisy for delivery of rescue and maintenance therapies especially for ambulatory patients. Literature review suggests bacterial contamination of nebulizers used by patients has often been described[15]. Even in most developed countries, an investigation of different components of nebulizer systems used at home showed that 50% of these components were contaminated[16]. The new generation, handy, portable, noise-free vibrating mesh nebulizers offer minimal intervention with regular hygiene of the medication cup on every use

The results of the current studies with active VMN the mean values for fine particle dose (FPD) and Fine particle fraction (FPF) from APSD testing are well within the specified limits including 85 to 115% of the emitted dose from the compressor air nebulizer[17].The results are also comparable to the APSD testing and results for Glycopyrronium nebulizing solution tested for delivery with eFLOW*Closed System nebulizer that is available in the international market[18,19].

The observed results for FPF (≥50%) ensures optimal efficiency with active VMN and compressor air nebulizer for delivery of Nebulizing Suspension/s during acute exacerbation or maintenance therapy in stable cases. Negligible residual volume with zero dilution factor further complements the clinical rationality and utility of active VMN for Home nebulization for delivery of rescue or maintenance medications.

The results need to be further evaluated in large pivotal clinical trials to further assess the clinical impact of the dual or triple drug combination aerosol delivery kinetics or lung deposition on clinical endpoints in High risk COPD cases as maintenance therapy. Although both CEN and USP [601] recommend the aerosol characterization for nebulizing formulations with 15L/min flow rate, the results with the current study are incremental in mimicking the real world practice of pMDI or VMN attachment to proximal arm of non-invasive ventilation (NIV) that may hamper the smooth inhalation of the Soft mist generated subsequently for adequate inhalation in such cases on BiPAP or IPAP/EPAP airflow maneuvers[20,21].

The current study was therefore conducted using ACI at 30 L/min, (Copley Scientific), patients of AECOPD during acute or post discharge phase of moderate or severe exacerbation[21,22].

CONCLUSION

The optimal APSD for Glycopyrronium nebulizing solution admixture with Formoterol/Budesonide suspension delivered through VMN and Compressor air nebulizer offers a clinically relevant strategy for High risk COPD cases in Acute or Home settings

Conflict of interest: The authors declare that there are no conflicts of interest to publish this paper.

Disclosure: The *in vitro* lung deposition study using Anderson Cascade impactor was supported by Academic grant from Glenmark Pharmaceuticals Ltd, Mumbai, India.

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