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Comparative pharmacokinetics of salbutamol inhaled from a pressurized metered dose inhaler either alone or connected to a newly enhanced spacer design

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ABSTRACT

Background: Coordination between actuation of a pressurized metered dose inhaler (pMDI) and inhalation is a critical manoeuvre that many patients fail to perform correctly. pMDIs connected to spacers do not require hand-lung coordination. This study evaluated the relative lung and systemic bioavailability and oropharyngeal deposition of salbutamol post-inhalation from Ventolin® Evohaler® (GlaxoSmithKline) either alone following verbal inhaler technique counselling (VC) or connected to a newly improved Able Spacer® (AS).

Methods: In a two-period, randomized crossover study, 16 healthy adults inhaled 2 × 100 μg salbutamol puffs (1 min gap) from Ventolin using VC or AS. Immediately after each puff inhalation, each subject gargled with 20 mL water for oropharyngeal deposition (OD) determination. Urine samples were collected 0.5 h (pre-) and 0.5, 1.0 and 2.0 h post-inhalation. Urine was then pooled 2–24 h post-inhalation. The relative lung bioavailability (0–0.5 h urinary salbutamol excretion – USAL0.5) and systemic bioavailability (0–24 h urinary excretion of salbutamol and its metabolite – USALMET24) were determined. A one week washout separated VC and AS use.

Results: The mean (SD) USAL0.5 of VC and AS was 5.36 (4.48) and 12.80 (10.83) μg, respectively. The mean (SD) OD was 11.35 (3.37) and 0.48 (0.30) μg, respectively. VC and AS were significantly different in USAL0.5 and OD ($p < 0.001$). USALMET24 was comparable ($p > 0.05$).

Conclusions: Compared with VC, AS doubled the inhaled salbutamol lung dose and minimised its precipitation in the oral cavity. The results suggest this inhalation aid can add therapeutic and safety benefits particularly in patients with continued pMDI technique issues despite repeated VC.

1. Introduction

The inhaled products' market has expanded enormously over time. Pressurized metered dose inhalers (pMDIs) and dry powder inhalers of various design and pharmaceutical formulation have been introduced [1]. However, the pMDI remains a fundamental inhaler for patients with obstructive lung conditions [2]. Many patients, however, do not get the maximal therapeutic benefit from their inhaled medicines because they fail to use their pMDIs correctly [3–5]. Up to 93% of patients have a hand-lung coordination issue which is expressed as an inability to press the canister at or instantly after the start of a slow inhalation through their pressurized inhaler [6]. This poor pMDI technique reduces lung deposition and maximises unwanted oropharyngeal deposition of inhaled medicines [2].

Verbal inhaler technique counselling (VC) improves patients' pMDI use [7, 8]. Despite repeated VC, many patients continue to misuse their pMDIs [9, 10]. Accordingly, these patients are usually prescribed spacer devices, also known as valved holding chambers (VHCs), to use with their pMDIs to overcome coordination and improper inhalation flow problems [3]. These add-on chambers slow the speed of the emitted aerosol particles giving more time for the patient to inhale the puff slowly and deeply. Additionally, spacers allow more evaporation of the aerosol propellant reducing the size of the drug particles and thus their impaction in the mouth and throat [11–13]. Available spacers differ in size, shape and engineering design. It has been reported that aerosol emission and particle size distribution vary between different spacers,

Study Registration: The study was prospectively registered with the ISRCTN registry (Reference: ISRCTN88332465)

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and within a particular spacer when used with different active pharmaceutical ingredients and formulations [14–16]. Able Spacer® (AS) (Clement Clarke International Limited, UK) is a small-size VHC that has recently been improved with the use of a special transparent polymer that incorporates silver ion anti-microbial technology to protect from contamination and inhibit microbial growth. The Spacer valve has been improved to operate at the low inhalation rates typical of the tidal flows of younger patients, combined with a visible valve movement that allows healthcare professionals to observe and confirm correct pMDI actuation and inhalation.

Various pharmacokinetic and gamma scintigraphy methods have been developed to determine the amount of a drug delivered to the lungs post-inhalation [17]. A urinary pharmacokinetic approach has shown that unchanged salbutamol excreted in urine within the first 30 min following dose inhalation (USAL0.5) represents the therapeutically effective lung dose (or relative lung bioavailability). Whilst, the cumulative renally-excreted salbutamol and its sulphate ester metabolite 0 to 24 h post dose inhalation (USALMET24) identifies the relative bioavailability of salbutamol to the body (the systemic exposure through both pulmonary and gastrointestinal tract (GIT) gates) [18]. This urinary salbutamol excretion pharmacokinetic approach has been applied to assess different pMDI inhalation methods [19, 20], VHCs [21, 22] and inhaler devices [23–25]. The current study evaluated and compared the relative lung (USAL0.5) and systemic (USALMET24) bioavailability of salbutamol inhaled by healthy adults from Ventolin® Evohaler® (GlaxoSmithKline) either alone following VC or connected to AS. The oropharyngeal deposition of salbutamol was also determined immediately post VC and AS inhalation.

2. Materials and methods

This was an investigational, two-period, two-sequence, randomized crossover pharmacokinetic study to assess two pMDI inhalation approaches on the relative lung and systemic bioavailability as well as the oropharyngeal deposition of inhaled salbutamol in healthy, adult male subjects. These approaches were using the pMDI either alone following VC or connected to AS. Ventolin® Evohaler® (100 μg salbutamol/puff, GlaxoSmithKline) was used as the pMDI. A one week washout separated the VC and AS inhalation approaches. Research ethical committee (REC) approval was obtained (Jordan Food and Drug Administration (JFDA) Ref.: 2/4/37/32225 (31–07–2017); and REC Ref.: 694–2017/V04-12/03/17). The study was prospectively registered at the ISRCTN registry (Reference: ISRCTN88332465). The study was conducted according to the International Council for Harmonisation Good Clinical Practice Guidelines.

All participants were 18 to 50 year-old males, non-smokers, signed their informed consent and were healthy as per the outcomes of the medical assessment, physical examination and biomedical laboratory tests done at recruitment. Subjects were excluded from participation if they had acute or chronic disease conditions, were using prescribed medications, alcoholics, drug addicts, or unable to understand and follow the study procedures. All participants were instructed to abstain from consuming any alcohols, caffeine- and xanthine-containing beverages or foods two days before and until 24 h after salbutamol administration. Additionally, they were instructed not to take any nutritional supplements or over the counter drug products one week before the beginning of the first study period and until their participation was complete. For safety purposes, vital signs (heart rate and blood pressure) and body temperature were recorded 1 h (pre-) and 15, 45 and 120 min post drug administration. Any adverse effects experienced by the subjects during each study period were recorded. Additionally, lung function assessed by forced expiratory volume in 1 s as percent predicted (FEV_1% predicted) was measured approximately 1 h (pre-) and 2 h post salbutamol inhalation. All subjects were medically and clinically reassessed (including vital signs, electrocardiogram, haematology and biochemistry laboratory tests) at discharge from each period.

In each study period, all volunteers were confined in the clinical site 12 h before and until 24 h after drug administration. Each participant was rigorously trained on their assigned inhalation method, and was subsequently allowed to demonstrate their trained inhalation approach using a placebo pMDI either alone (VC) or connected to AS (according to randomisation) until satisfactory inhalation technique was achieved. The participants' peak inhalation flow (PIF) through the pMDI (± AS) was then checked using an In-Check Dial® flow meter (Clement Clarke International Limited, UK) to ensure a slow inhalation between 30 and 60 L/min. PIFs > 60 L/min mandated repeating VC or AS training until acceptable PIFs were achieved. Subjects randomized to VC were verbally trained to shake the inhaler first, breathe out comfortably to empty their lungs, place the pMDI mouthpiece tightly between their lips, start a slow inhalation and then immediately press the canister to release a puff, continue flawlessly the slow and deep inhalation manoeuvre for up to 5 s before removing the pMDI from their mouth and holding their breath for up to 10 s. Subjects randomized to AS use were trained to use the pMDI plus AS according to the instructions in the patient information leaflet focusing on the slow and deep inhalation and the subsequent breath holding manoeuvres. Before drug administration, Ventolin pMDIs (± AS) were prepared for use according to the manufacturers' instructions. On the day before drug administration and to reduce inner surface electrostatic charge, AS devices were dipped in lukewarm liquid dishwashing detergent solution and allowed to completely air dry.

Each volunteer inhaled 2 × 100 μg puffs from a Ventolin Evohaler separated by 30–60 s using the assigned VC or AS approach. Immediately after each puff inhalation, the volunteer mouth-washed and gargled with 20 mL water which were combined, stored (−20 °C) and assayed later for salbutamol. Each volunteer emptied their bladder 0.5 h before drug administration (pre-treatment urine sample). Urine samples were then collected 0.5, 1.0 and 2.0 h post salbutamol inhalation. Subsequently, each volunteer pooled their urine 2–24 h post salbutamol inhalation. The volume and pH of each urine sample were recorded. All urine samples were stored at −20 °C until extracted and analysed by an in-house developed and validated high performance liquid chromatography-tandem mass spectroscopy (HPLC-MS/MS) technique. The salbutamol relative lung bioavailability was determined by the recovered amount of unchanged salbutamol in urine 0–0.5 h post-inhalation (USAL0.5). Urine samples collected 0.5 to 24 h post-inhalation were assayed twice; for unchanged salbutamol and for total salbutamol (unchanged plus its sulphate ester metabolite). The total amount of unchanged salbutamol plus metabolite recovered from urine 0–24 h post inhalation (USALMET24) identified the relative systemic bioavailability of salbutamol. Oropharyngeal deposition of the inhaled salbutamol was evaluated by analysing the mouthwash aqueous samples.

2.1. Salbutamol quantitation

An HPLC-MS/MS method has been developed and validated for determining the concentration of salbutamol in urine and mouthwash samples. Instrumentation comprised an Agilent 1200 series HPLC isocratic pump, Agilent 1260 series in-line degasser, Agilent 1200 series auto-sampler, and Agilent 1200 series column oven (Aligent, Santa Clara, CA, USA). The MS/MS detector was Applied BioSystem API 4000 Triple Quadrupole tandem mass spectrometer (MDS Sciex, Ontario, Canada). In summary, salbutamol and salbutamol-D9 acetate (internal standard), batch ID: CS-SI-AAA-0735–01, Clearsynth Labs Ltd., Mumbai, India) were resolved using a mobile phase consisting of acetonitrile and 10 mM ammonium formate (30:70 v/v) on an ACE® C_{18} (100 × 4.6 mm, 5 μm) column in an isocratic mode. The method was accurate, precise, stable and linear over a salbutamol concentration range between 5 and 1000 ng/mL.

Using a solid phase extraction (SPE) technique, unchanged salbutamol in all collected urine samples was extracted using OASIS® HLB

30 mg sorbent in 1 mL cartridges (Waters GmbH, Vienna, Austria). To quantify the total salbutamol (unchanged salbutamol plus its metabolite) in urine samples collected at 1, 2 and 2–24 h post salbutamol inhalation, the samples were first acid hydrolysed (0.1 N HCL for 1 h at 60 °C) to convert all metabolised salbutamol back to the free salbutamol. The samples were then cooled to room temperature and neutralised before they were extracted using OASIS® HLB cartridges. A 5 μL volume of each extracted and reconstituted sample was injected into the HPLC-MS/MS for salbutamol quantification. The subjects' mouthwash samples were assayed directly without SPE by the HPLC-MS/MS method after adding internal standard and dilution processing.

2.2. Statistical analysis

Statistical analysis of the study results was carried out using the Statistical Package for Social Sciences software (IBM SPSS for Windows, Version 20). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check for normality of the data. Comparisons of the study outcome measures between the VC and AS inhalation methods were performed using the Wilcoxon test (non-parametric data). A p-value < 0.05 was considered statistically significant for any difference.

3. Results

Sixteen healthy male subjects with mean (SD) age, height, weight and body mass index (BMI) of 29.4 (9.7) years, 1.80 (0.1) m, 81.4 (15.2) kg and 25.4 (3.7) kg/m^2, respectively, took part in the study. All participants had normal medical, physical and laboratory examinations at study completion, and no-one reported any adverse effects. The mean (SD) PIFs through pMDI following VC and AS training were 45.6 (9.8) and 47.5 (8.8) L/min, respectively, with no significant difference (Wilcoxon $Z = -0.52$; $p = 0.602$). The pH of all urine samples ranged between 5 and 7.5. It is unlikely that salbutamol exhibits significant pH-dependent renal clearance [18, 26].

The mean (SD) amounts of unchanged salbutamol deposited in the mouth and throat, as well as that renally-excreted 0.5, 1.0, 2.0 h and subsequently until 24 h post VC and AS inhalations are summarised in Table 1. The mean (SD) of total salbutamol (salbutamol and its metabolite) excreted in urine 0.5 to 24 h post salbutamol inhalation is shown in Table 2. Individual oropharyngeal deposition, relative lung bioavailability (USAL0.5) and systemic bioavailability (USALMET24) following VC and AS are presented in Figs. 1–3, respectively. Wilcoxon comparisons between VC and AS showed significant differences in oropharyngeal deposition (Wilcoxon $Z = -3.52$ ($p < 0.001$)) and in USAL0.5 (Wilcoxon $Z = -3.21$ ($p = 0.001$)). The two inhalation methods, however, resulted in comparable USALMET24 (Wilcoxon $Z = -1.65$ ($p = 0.100$)). It is noteworthy that the statistical significance of the oropharyngeal deposition, USAL0.5 and USALMET24 was not affected when the statistical comparisons were repeated excluding the results of subject No. 11 (USAL0.5 AS outlier, Fig. 2).

Regarding lung function, the mean (SD) baseline FEV_1% predicted prior to VC and AS salbutamol inhalation was 94.8 (8.9) and 96.1 (11.2)%, respectively. Mean (SD) FEV_1% predicted measured two hours post inhalation was 97.4 (9.9) and 97.6 (11.6)%, respectively. The FEV_1% predicted pre- and post-salbutamol administration were statistically similar within the VC and AS; Wilcoxon $Z = -1.20$ ($p = 0.232$) and $Z = -1.05$ ($p = 0.292$), respectively.

4. Discussion

Lung deposition of orally inhaled medicines is critical to achieve the desired therapeutic outcome. The amount of drug that reaches the distal areas of the lungs, where the sites of pharmacologic action are, depends on the prescribed inhaler device, aerosol emission and particle size characteristics and, equally important, the patient's mastery in inhaler technique and inhalation [27]. It has been reported that up to 30% of inhaled salbutamol is delivered to the lungs [17]. The remaining percent generally impacts in the mouth and throat, is subsequently swallowed and absorbed from the GIT into the systemic circulation which potentially affects the safety profile of the drug. Sixteen healthy, adult males took part in this study to evaluate the fate of salbutamol inhaled from Ventolin Evohaler either alone following VC or connected to the recently improved AS.

Spacers are used to overcome hand-lung coordination and overly fast PIF. These add-on inhalation accessories are generally known to improve the lung dose, but do so to varying extent [28]. In this study, connecting AS to Ventolin Evohaler doubled salbutamol delivery to the lungs compared with the VC solo pMDI use (mean USAL0.5 (% nominal dose): 12.80 μg (6.4%) and 5.36 μg (2.7%), respectively). Our findings are consistent with previous 30-minute urinary salbutamol pharmacokinetic data: Ventolin pMDI alone (5.7 μg (2.8%), connected to large Volumatic® spacer (16.4 μg (8.2%) and small AeroChamber Plus® spacer (14.8 μg (7.4%) [21]. A similar trend of the positive impact of spacers on lung delivery has also been observed in other studies [12, 22]. In real-life, VC improves pMDI technique and inhalation [7, 8, 29]. However, the benefit of VC fades with time and patients revert to their poor inhaler use. A significant reduction in USAL0.5 was previously reported when asthmatic patients inhaled 1 × 100 μg puff slowly (2.67 μg) versus fast (1.90 μg) through Ventolin pMDI [20]. Our subjects received rigorous VC on correct pMDI technique and were also closely observed during salbutamol inhalation, hence their higher relative lung bioavailability compared with that previously reported in poor inhaler users [20]. The present findings, therefore, confirm the importance that patients prescribed pMDIs receive frequent VC during their routine clinic visits.

Oropharyngeal deposition of inhaled medicines decreases by up to 90% when VHCs are connected to pressurized inhalers [11, 30–32]. Inhalation of salbutamol through AS reduced oropharyngeal deposition by approximately 96% (AS mean (SD): 0.48 (0.3) μg versus VC mean (SD): 11.35 (3.4) μg). Since oropharyngeally deposited medicines are

Table 1
Mean (SD) amount (μg) of unmetabolized salbutamol recovered in the samples of 16 healthy volunteers after inhaling two puffs (100 μg each) of salbutamol.

Inhalation approach		Oropharyngeal deposition	Urinary recovery of unchanged salbutamol (USAL) in the given time period (hr)				
			USAL0.5 (0–0.5 hr)	USAL (0.5–1 hr)	USAL (1–2 hr)	USAL (2–24 hr)	Cumulative USAL (0.5–24 hr)
VC (pMDI alone)	Mean (SD), μg	11.35 (3.37)	5.36 (4.48)	3.50 (2.16)	5.83 (3.58)	26.46 (19.48)	35.79 (23.09)
	% of nominal dose (SD)	5.67 (1.69)	2.68 (2.24)	1.75 (1.08)	2.91 (1.79)	13.23 (9.74)	17.89 (11.55)
AS (pMDI + AS)	Mean (SD), μg	0.48 (0.30)	12.80 (10.83)	11.11 (7.05)	7.50 (4.75)	24.81 (13.86)	43.42 (20.53)
	% of nominal dose (SD)	0.24 (0.15)	6.40 (5.41)	5.55 (3.53)	3.75 (2.37)	12.40 (6.93)	21.71 (10.26)

$n = 15$ for USAL0.5–24 (VC period) as one subject withdrew about 5 hrs after drug administration due to a personal/family reason.
USAL0.5 represents relative lung bioavailability of inhaled salbutamol.

Table 2
Total salbutamol (salbutamol plus its metabolite) renally-recovered after inhaling two puffs (100 μg each) of salbutamol.

Inhalation approach		Urinary recovery of salbutamol plus its metabolite (USALMET) in the given time period (hr)				
		USALMET (0.5–1 hr)	USALMET (1–2 hr)	USALMET (2–24 hr)	Cumulative USALMET (0.5–24 hr)	USALMET24 (0–24 hr)
VC (pMDI alone)	Mean (SD), μg	4.84 (3.18)	7.33 (4.30)	32.26 (23.05)	44.43 (27.33)	50.12 (29.27)
	% of nominal dose (SD)	2.42 (1.59)	3.66 (2.15)	16.13 (11.52)	22.21 (13.67)	25.06 (14.64)
AS (pMDI + AS)	Mean (SD), μg	14.01 (7.59)	9.95 (6.29)	29.47 (15.00)	53.43 (23.02)	66.23 (27.63)
	% of nominal dose (SD)	7.00 (3.80)	4.98 (3.14)	14.74 (7.50)	26.71 (11.51)	33.12 (13.82)

USALMET24 = USAL0.5 plus USALMET0.5–24 (which represents the relative systemic bioavailability of inhaled salbutamol).
n = 15 (VC period) as one subject withdrew about 5 hrs after drug administration due to a personal/family reason.

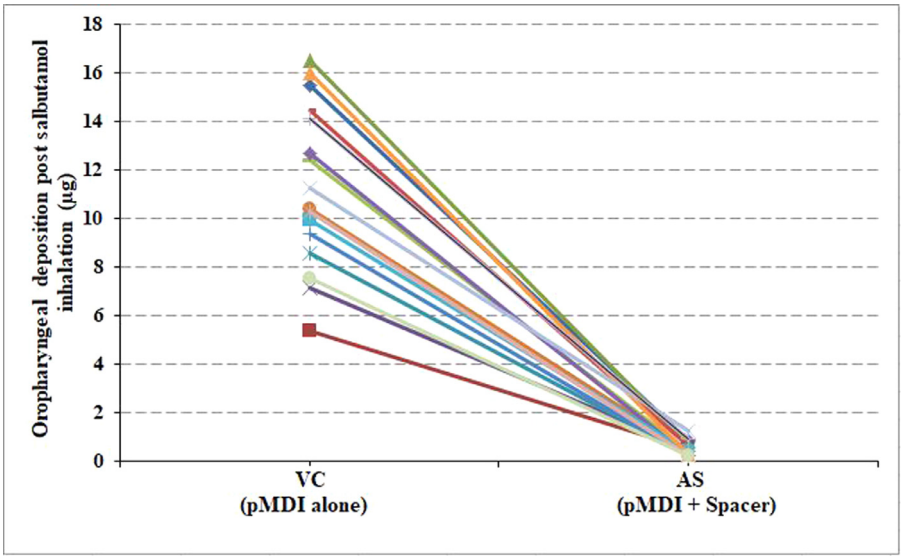

Fig. 1. Individual oropharyngeal deposition of post salbutamol (200 μg) inhalation.

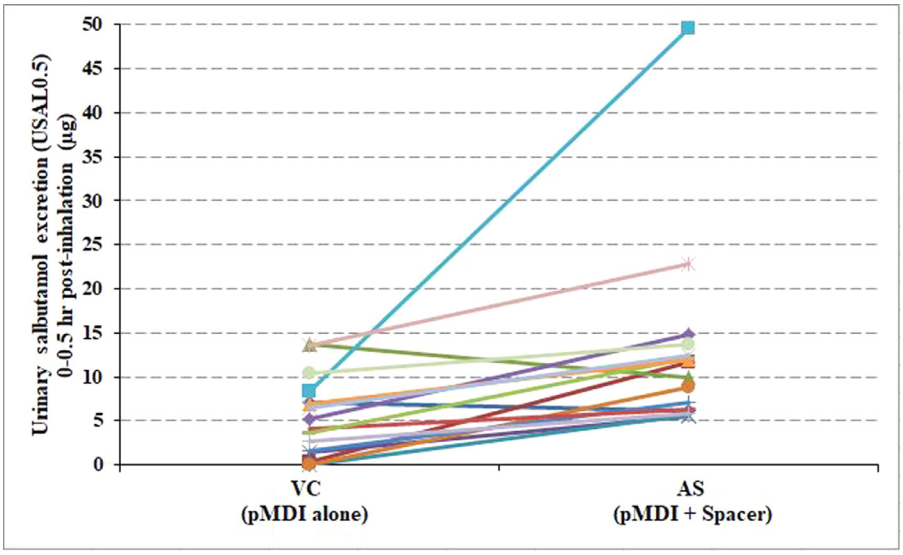

Fig. 2. Participants' renally excreted salbutamol over 30 min (USAL0.5) following VC and AS inhalation.

primarily swallowed and GIT-absorbed, reduced mouth and throat impaction decreases the risk of both local and systemic side effects [28].

Both VC and AS resulted in comparable relative salbutamol bioavailability to the body identified by USALMET24 alone and when oropharyngeally deposited salbutamol was considered. Similarly, inhalation through Volumatic and AeroChamber VHCs showed no difference in USALMET24 compared to inhalation from Ventolin pMDI alone [21]. On the other hand, Hindle and Chrystyn (1994) reported significant reductions in USALMET24 when Volumatic, Bricanyl and Nebuhaler chambers were used [22]. However, the subjects in this study inhaled double (4 × 100 μg) the usual dose used (2 × 100 μg) in clinical practice.

5. Conclusion

Poor pMDI technique is common among patients with respiratory

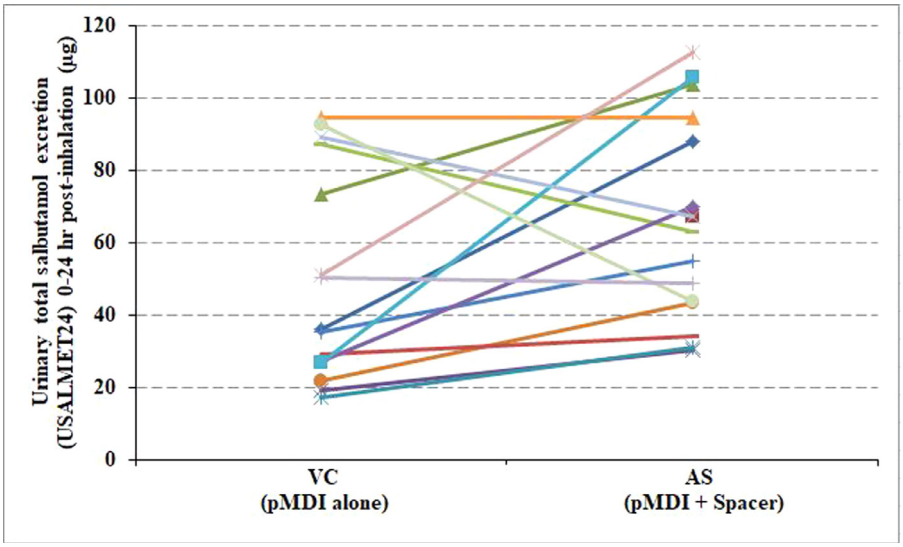

Fig. 3. Individual urinary excretion of total salbutamol (parent and its metabolite) 0–24 hr following VC and AS inhalation.

conditions. This has negative consequences on the therapeutic outcomes of the pMDI therapy. VC is vital and has improved the lung dose from Ventolin Evohaler. However, adding AS to Ventolin Evohaler has doubled the pulmonary salbutamol bioavailability and almost diminished drug precipitation in the oral cavity. In addition to its recent antimicrobial growth technology and inhalation valve design improvements, AS can provide extra therapeutic and safety benefits particularly in patients with continued pMDI technique issues despite repeated VC.

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Declaration of Competing Interest

W.G.A. is an Academic Researcher in the inhaled respiratory medicine and inhaler devices areas. He has received unconditional travel grants from Clement Clarke International Limited to present his research work at ATS, BTS, ERS and ISAM conferences.

G.A.O. has no conflict of interest to declare.

M.S. is the Chief Technology Officer (CTO) at Clement Clarke International Limited, UK.

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