Understanding flow rate influence on Clip-Tone guided inhaler delivery.

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Summary

Clip-Tone® is a novel add-on to a pressurised metered dose inhaler (pMDI) that provides the patient with an acoustic signal during their use of the inhaler. The signal is intended to help patients establish good inhaler technique in respect of inspiratory flow rate, coordination and duration of inhalation. It is important to understand whether such devices have an impact on inhaler delivery performance. We have conducted a series of assessments to determine any effects: these have included aerosol particle size determinations (APSD) and aerosol characteristics at three flow rates (20, 30 and 48 L.min^{-1}) that represent the range of the acoustic signal and plume geometry assessment at 30 L.min^{-1}. All assessments were made with standard Ventolin® Evohaler® (100µg salbutamol, GSK) with and without (Control) the Clip-Tone device. Fine particle fraction data (%<5µm) at 20, 30 and 48 L/min for Control were 27.5±2.0, 48.9±1.3 and 43.8±2.9 respectively; for pMDI plus Clip-Tone: 30.0±1.7, 48.2±1.6 and 44.9±1.6. Similarly, fine particle dose data (µg<5µm) were Control: 27.8±3.5, 39.8±1.9 and 46.3±7.1 and pMDI plus Clip-Tone: 31.0±2.0, 41.5±2.5 and 40.9±3.1. Summary APSD data were comparable. Mean spray velocity and plume angle were not different between the test groups: 64.6±4.9 m.second^{-1} and 10.2°±4.8 for Control and 63.8±6.7 m.second^{-1} and 11.5°±5.7 for pMDI with Clip-Tone, respectively: any variation in results between tests conducted was less than the natural spray-to-spray variability of the inhaler. APSD, aerosol characteristics and plume geometry have demonstrated that the Clip-Tone inhaler technique guidance device is without clinical impact on aerosol delivery.

Key Message

Inhaler technique is of paramount importance. A new acoustic-signal training tool that encompasses flow rate, coordination and duration, and is for continual use (ie. during drug administration) is without clinical impact on aerosol characteristics while the signal sounds and does not affect the aerosol plume.

Introduction

There are numerous inhaler technique training aids that help healthcare professionals explain inhaler use to patients.[1] In the UK there are only two training tools that can be applied to the active inhaler to guide patients: the Flo-Tone® and the newer Clip-Tone® device [2,3]. The Clip-Tone has the singular advantage that, as a simple retrofit tool, it can remain affixed to the pressurised metered dose inhaler (pMDI) actuator (not the mouthpiece) and provide daily guidance (Figure 1). The device produces an audible signal as the patient inhales, which helps to achieve the correct flow rate, coordinate actuation and maintain an adequate duration of inhalation. The acoustic signal is produced between flow rates of 20 and 48 L.min^{-1}. It was therefore important to conduct appropriate testing at these flow rates in addition to the *in vitro* standard of 30 L.min^{-1} in order to identify any potential impact of the addition of the Clip-Tone device to the pMDI. Aerosol particle size distribution (APSD) determinations at 30 L.min^{-1} have already been conducted with Clip-Tone use across a range of single, dual and triple therapies [2]. We therefore extended these evaluations to include the flow rate span at which the guidance-whistle sounds. In addition, we have evaluated plume geometry from pMDI plus Clip-Tone, compared with pMDI alone. Plume geometry is a key Food and Drug Administration (FDA) metric for pMDI bioequivalence and a critical attribute for pMDI actuation quality and consistency [4]. We believe this type of research has not before been carried out with an inhaler training aid. Although the device is not mouthpiece-mounted, we consider it important to determine any effect, given the potential for the device to be used habitually.

Figure 1 – pMDI plus Clip-Tone

Experimental Methods

The pMDI spray analysis (high-speed sample imaging, plume angle and spray velocity) was conducted at the LTRAC, Department of Mechanical & Aerospace Engineering, Monash University, Australia; https://ltrac.eng.monash.edu.au) [5,6] and the aerodynamic particle size distribution research was carried out at i2c Pharma Services (Cardiff Medicentre, Cardiff, UK: http://www.i2cpharm.co.uk).

Aerosol particle size distribution data (APSD) and aerosol characteristics of Ventolin Evohaler pMDIs with or without (Control) the Clip-Tone device (n=5) were determined using a Next Generation Impactor (NGI, Copley

Scientific, UK) operated at 20 and 48 L.min^{-1}. pMDIs were primed according to the patient information leaflet. Once primed the pMDI was held in an upright position and shaken for 5 seconds (approximately 3 shakes per second) with the valve maintained in a downward position at all times. Immediately following shaking the pMDI was actuated, via an adaptor into the inlet port of the NGI, by quickly depressing the canister with the thumb and holding for 1 second before releasing. This process was repeated until five actuations were delivered. The actuation cycle was performed with and without the Clip-Tone attached to the pMDI. Following dose deposition, the NGI components were quantitatively washed with recovery solution to obtain salbutamol. Samples were placed on a gentle rocker for 5 minutes to ensure accurate recovery of the drug. Clip-Tone was placed in a beaker and sonicated for 3 minutes. Salbutamol quantification was performed using a validated HPLC method (Aligent Technologies UK Limited, Cheadle, UK). Salbutamol values were reported as salbutamol base. Metered and emitted dose, fine particle fraction (FPF, %<5.0μm), fine particle dose (FPD, μm<5.0μm), mass median diameter (MMAD, μm) and geometric standard deviation (GSD, σg) were determined. The presence of an audible training-whistle tone was monitored. Data from previous i2c Pharma NGI research with Ventolin Evohaler pMDI with (n=5) and without Clip-Tone (n=3) operated at 30 L.min^{-1} [7] are included.

A salbutamol pMDI (Ventolin® Evohaler®) was carriage-mounted below a solenoid plunger and firmly supported in the focal plane of the imaging system (Figure 2). Experiments were conducted without (Control) and with the Clip-Tone device *in situ*. Apparatus that might otherwise have been used to simulate an inhalation manoeuvre (e.g. a vacuum vessel) was not suited to a clear area for spray imaging. To maintain realistic conditions, a small positive air pressure (dry compressed air at 22°C) was applied to the top of the inhaler, via an air-tight seal, and the total flow rate entering the top of the inhaler was measured to produce an equivalent inspiration rate of 30 L.min^{-1}. pMDI nozzle-exit flow velocity (9mm downstream the mouthpiece) was measured with a turbine rotameter to check that the average of the combined flow velocity around the spray was consistent between tests. The imaging system comprised a Chronos 1.4 high speed camera (Kron Technologies, Inc.) with LUX1310 complementary metal-oxide-semiconductor (CMOS) sensor (Luxima Technology LLC) [8] and Navitar MVL7000 zoom lens (Navitar, Inc.), giving a focal plane resolution of 36 pixels.mm^{-1} (28 μm.pixel^{-1}). The light source was a custom high-current pulsed LED module producing 250 nsecond pulses [9], collimated into a beam using an f=60mm macro lens.

High-speed spray analysis sample images and plume angle tests (n=32 per group) were obtained at 1,600 frames.second^{-1} with a sufficiently large field of view to capture the entire spray. Images were post-processed to negate background effects, and rendered in false colour. Each plume angle test contained 2,400 images with 800 width measurements per image (1.92 million width measurements per spray). Spray velocity was measured by tracking large liquid structures in the spray plume (not the velocity of the vapour phase), and measuring their displacement between images. Each velocity test (n=8 per group) contained 12,500 images. Detailed test conditions and algorithms for quantitating spray angle and velocity are available from the authors.

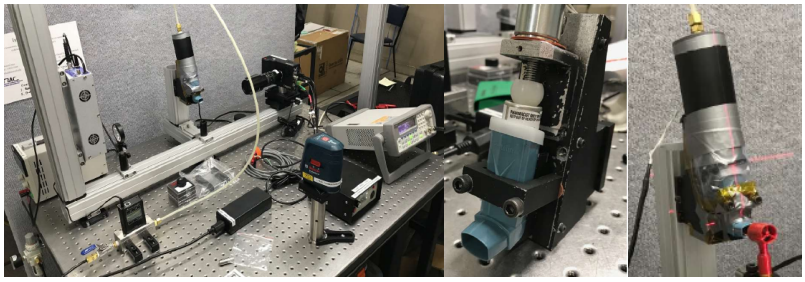

Figure 2 – (left) Spray analysis experimental apparatus: LED on the left, inhaler in the centre, camera on the right; (middle) pMDI plus Clip-Tone and solenoid plunger; (right) turbine rotameter in front of the pMDI mouthpiece.

Results

A clear audible signal was produced at the different flow rates during the APSD experiments. Within a flow rate, aerosol characteristic data were directly comparable between pMDIs irrespective of the presence of the Clip-Tone device (Table 1), with the exception of the emitted dose data at 48 L.min^{-1}. The mass balance recovery of salbutamol at this flow rate was, however, within acceptable limits (±25% of metered dose).

Variable	20 L.min^{-1}		30 L.min^{-1} [7]		48 L.min^{-1}	
	VE Control	VE plus Clip-Tone	VE Control	VE plus Clip-Tone	VE Control	VE plus Clip-Tone
Metered Dose (μg)	118.6 ± 6.7	120.2 ± 4.8	93.9 ± 4.7	98.0 ± 5.1	119.4 ± 16.1	103.6 ± 4.0
Emitted Dose (μg)	100.7 ± 6.2	103.6 ± 4.7	82.6 ± 5.0	86.0 ± 3.8	105.7 ± 14.3	91.6 ± 4.1
FPF (%<5μm)	27.5 ± 2.0	30.0 ± 1.7	48.9 ± 1.3	48.2 ± 1.6	43.8 ± 2.9	44.9 ± 1.6
FPD (μg<5μm)	27.8 ± 3.5	31.0 ± 2.0	39.8 ± 1.9	41.5 ± 2.5	46.3 ± 7.1	40.9 ± 3.1
On Actuator (μg)	17.9 ± 1.5	16.7 ± 1.6	11.3 ± 0.7	12.0 ± 1.5	13.7 ± 2.0	12.0 ± 0.6

Table 1 – Aerosol characteristics of salbutamol from Ventolin Evohaler (VE) with and without Clip-Tone (Control)

The summary of salbutamol APSD data are presented in Figure 3. Within all three flow rates, the NGI distributions between pMDI alone and pMDI with Clip-Tone were comparable. Individual NGI stage data are available from the authors. There was no recovery of salbutamol from the Clip-Tone: either owing to the absence of the device or because it was located on the top of the actuator, physically before the point of aerosol release.

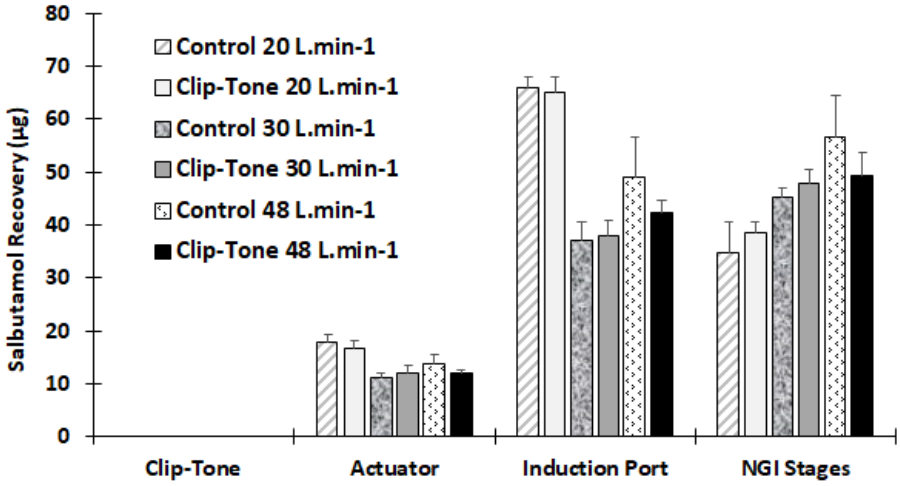

Figure 4 – Aerosol particle size distribution for test components and NGI (mean±SD, µg)

The apparatus set-up for Control pMDI imaging required approximately 8kPa above atmospheric pressure (atm), to correspond to a mouthpiece flow velocity of 1.3±0.1 m.second^{-1} (30±0.5 L.min^{-1}). To achieve the same velocity, the set-up for pMDI plus Clip-Tone necessitated 26kPa above atm. Once the pressure exceeded 23kPa, the Clip-Tone made an audible whistling sound, confirming that the experiments were operating within the correct range of flow rates for training device and pMDI function.

In the sample spray analysis images of pMDI plus Clip-Tone (Figure 4, 7.100 to 14.375 mseconds), the spray travels from right to left; the dark object on the right-hand side of each image is the inhaler mouthpiece. Purple and black regions correspond to high droplet and particle density; white and yellow regions correspond to low density where light travels unimpeded through the spray.

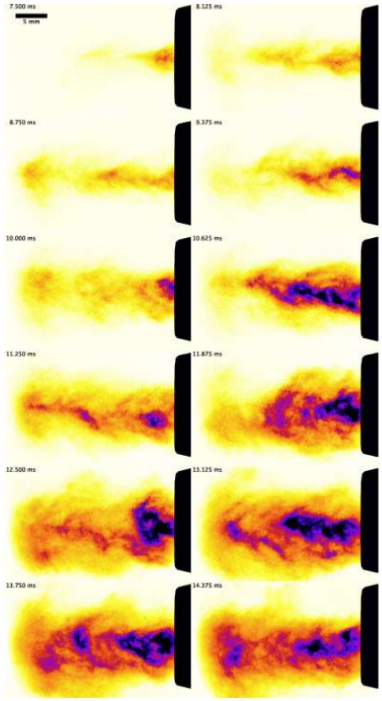

Figure 4 –High-speed spray image (pMDI plus ClipTone)

Test	Velocity ± SD (m.second^{-1})	
	pMDI plus Clip-Tone	pMDI Control
1	64.8 ± 6.0	63.9 ± 7.1
2	62.1 ± 7.9	64.3 ± 6.1
3	61.1 ± 6.5	65.7 ± 6.4
4	64.5 ± 6.8	65.8 ± 7.3
5	64.2 ± 6.9	63.3 ± 6.3
6	62.9 ± 6.7	67.3 ± 5.9
7	66.5 ± 6.7	61.7 ± 5.6
8	64.0 ± 6.7	64.5 ± 6.5
Mean	**63.8 ± 6.7**	**64.6 ± 4.9**

Table 2 – Spray velocity results

Weak spray or agglomerated particle images reduced the plume angle data set to n=22 for Control and n=17 with Clip-Tone. The mean plume angle for Control was 10.2 ± 4.8 degrees and for pMDI plus Clip-Tone 11.5 ± 5.7: a mean increase in plume angle of approximately 1.3° when Clip-Tone was used.

The mean spray velocity for the two groups was not significantly different: Control 64.6 ± 4.9 m.second^{-1} and for pMDI plus Clip-Tone 63.8 ± 6.7 m.second^{-1} (Table 2).

Discussion

The difference in the with/without Clip-Tone 48 L.min^{-1} emitted dose was attributed mainly to the higher recovery from the Control tests, rather than low recovery from the plus Clip-Tone experiments. The remaining key variable data were largely comparable within and across flow rates. There was a greater recovery of salbutamol in the induction port at the lowest 20 L.min^{-1} flow rate for both test groups however, with commensurately lower FPF and

FPD values. Although these aerosol characteristics differed between flow rates this was not unexpected or considered of clinical relevance [10], the dose of salbutamol being sufficient for clinical effect [11].

To create comparable experimental conditions between test groups for the spray analysis, a relatively large increase in atmospheric pressure was necessary: the absolute increase in upstream pressure was, however, only approximately 14%. Previous research has shown that use of the Clip-Tone adds minimally to pMDI resistance, and within that considered typical for pMDIs [12]. The spray imaging (Figure 4) is provided for demonstration of a typical false-colour output, whereas the spray angle and velocity results are based on multiple quantitative data. The increase in plume angle of 1.3° when the Clip-Tone device was used may correspond to a change in the airflow around the spray. Although the average velocity was constant between pMDI Control and pMDI plus Clip-Tone, the larger pressure drop across the latter may have altered the velocity profile. The plume angle difference is, however, small compared to the variability from shot-to-shot of approximately 5°. This is primarily a result of the unsteady nature of the spray and the presence of large-scale structures. On this basis, we believe the variation within each test group was not of significance. No significant differences were observed between the test groups for spray velocity, which are typical of those previously observed in pMDIs within 30mm of the nozzle.

Conclusion

With the availability of an inhaler guidance tool that can be applied to an active device it is important that adequate testing is conducted across the range of conditions that the patient may use the device to good effect. Clip-Tone has been developed to emit an acoustic guidance signal from 20-48 L/min: a range consistent with inhaler guidance. The results demonstrate that the provision of Clip-Tone guidance, despite a small increase in resistance, does not have a detrimental effect of the aerosol characteristics, or affect plume geometry as determined by plume angle and spray velocity.

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