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Breath-synchronized plume-control inhaler for pulmonary delivery of fluticasone propionate

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Abstract

A novel breath-synchronized, plume-control inhaler (Tempo™ inhaler) was developed to overcome limitations of a pressurized metered-dose inhaler. This report compared the Tempo inhaler and a commercial inhaler for fine particle distribution and lung deposition of fluticasone propionate. In vitro fine particle distribution was determined using the Andersen Cascade Impactor at inspiration rates of 28.3 and 45 L/min. In vivo lung deposition was assessed in a randomized, two-arm, crossover study of ^{99m}Tc-radiolabeled fluticasone propionate in 12 healthy adult subjects, analyzed by gamma scintigraphy. In vitro: fine particle fractions at 28.3 and 45 L/min were 88.6 ± 3.6% and 89.2 ± 3.0% (Tempo inhaler) versus 40.4 ± 4.7% and 43.1 ± 4.4% (commercial inhaler). In vivo: lung deposition was 41.5 ± 9.8% (Tempo inhaler) versus 13.8 ± 7.4% (commercial inhaler) and oropharyngeal deposition was 18.3 ± 7.7% (Tempo inhaler) versus 76.8 ± 7.1% (commercial inhaler). Variability of lung deposition was reduced from 55% (commercial inhaler) to 24% (Tempo inhaler) of the delivered dose. The Tempo inhaler produced significantly higher fine particle fraction values, reduced oropharyngeal deposition by 75%, and increased whole, central, intermediate, and peripheral lung delivery by more than 200%. Thus, the Tempo inhaler enhances efficient drug delivery to the lungs.

Keywords: Aerosol drug delivery; Fluticasone propionate; Breath-synchronized plume-control inhaler; Lung deposition

1. Introduction

Inhaled corticosteroids (ICS) are a standard of care for the treatment of asthma, and devices for optimal delivery of corticosteroids to the lungs continue to evolve (Barnes et al., 1998). The pressurized metered-dose inhaler (pMDI) has been widely adopted for delivery of drugs, and this device is recommended as the first choice for routine delivery of ICS (Brocklebank et al., 2001). Despite their widespread use, however, efficient drug delivery with a pMDI is often limited by poor user coordination, wide dose to dose variation and by high oropharyngeal and low and inconsistent pulmonary deposition of drug (Borgström et al., 2000; Newman, 2005; Rau, 2005). One consequence of high oropharyngeal deposition of ICS is an increased incidence of local side effects including throat irritation, dysphonia, and candidiasis (Barnes et al., 1998; Roland et al., 2004). A need exists for improved devices for delivery of ICS and other drugs that will optimize pulmonary delivery and minimize oropharyngeal deposition.

One option is breath-actuated devices, which automatically release a dose of drug upon forced inhalation and eliminate reliance on patient coordination for effective aerosol delivery (Newman et al., 1991; Hampson and Mueller, 1994). A study of over 5000 patients showed that breath-actuated devices provided better symptomatic control than standard pMDIs, reduced extra medication requirements, and reduced visits to healthcare practitioners or outpatient clinics (Price et al., 2003). However, available breath-actuated pMDIs suffer from being flow rate dependant for the trigger to discharge a dose from the metering valve, and the emitted plume still leaves the mouthpiece at high velocity (∼50 miles/h) resulting in oropharyngeal impaction (Newman, 2005). This has led to the development of "spacers"; valve holding chambers, which attempt to capture

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the plume in variable volume chambers, allowing some drug to impact on the inner walls of the chamber (instead of a patient's throat) (Bisgaard et al., 2002). However, these devices are generally separate from the pMDI and often bulky, two factors which often lead to their under use even when prescribed in routine care and may still result in wide dose to dose variation in drug delivery.

A novel breath-synchronized, plume-control inhaler, the Tempo inhaler, was developed to overcome the limitations of existing breath-actuated devices (Armer et al., 2007). The Tempo inhaler incorporates a novel, patented, breath synchronous trigger that automatically, and without the use of any electronics, adjusts the trigger to actuate based on the fraction of the inhaled breath volume which is preset for an individual drug, and automatically adjusted for the rate of inhalation for an individual breath (Fig. 1). Another novel feature of the Tempo inhaler is a flow control chamber which slows emitted drug plumes down to ∼10% of their emission velocity from the canister while spinning the slowly expanding plume into a vortex. These features help ensure that a greater fine particle fraction of drug is delivered to the respiratory tract at the pre-specified time in the inspiratory cycle determined by the setting on the breath synchronous trigger.

For drugs targeting systemic delivery, the Tempo inhaler is tuned to release the dose early in the inspiratory cycle so that drug can be drawn deep into the lung. If conducting airway deposition is required, the trigger can be tuned to release later in the inspiratory cycle so that the lungs have partially filled with air and drug can be predictably delivered to the conducting airways.

The objective of this study was to assess the performance of the Tempo inhaler compared with a pMDI used with the standard commercial actuator for pulmonary delivery of fluticasone propionate (FP) using in vitro (via inertial impaction) and in vivo (via gamma scintigraphy) methods. Radionuclide imaging data can provide a useful assessment of new inhalers, acting as a bridge between in vitro testing, supplemented by pharmacokinetic data and full clinical trials programs (Newman et al., 2000, 2003). Furthermore, safety of this altered delivery through the Tempo inhaler in humans was assessed from vital signs and reports of adverse events.

2. Methods

2.1. In vitro study

The in vitro methods comprised characterization of fine particle distribution (Pitcairn and Newman, 1997; Dunbar and Mitchell, 2005) using the Andersen Cascade Impactor at constant airflow rates of 28.3 and 45.0 L/min, where mass was analyzed using high performance liquid chromatography (HPLC). Fluticasone proprionate plasma levels were determined over a range of 0.25–20 μg/mL. A suitable HPLC was fitted with a thermostatted column compartment, UV detector, and integrator/data station. A Phenomenex, Luna, $C_{18}(2)$, 5 μm, 150 mm × 4.6 mm or equivalent HPLC column was used with an injection volume of 20 μL, a flow rate of 0.70 mL/min, a temperature of 25 °C, a detection wavelength of 240 nm, and an approximate run time of 10 min. The relative standard deviation was not more than 3.0%, and accuracy was within 98–102%.

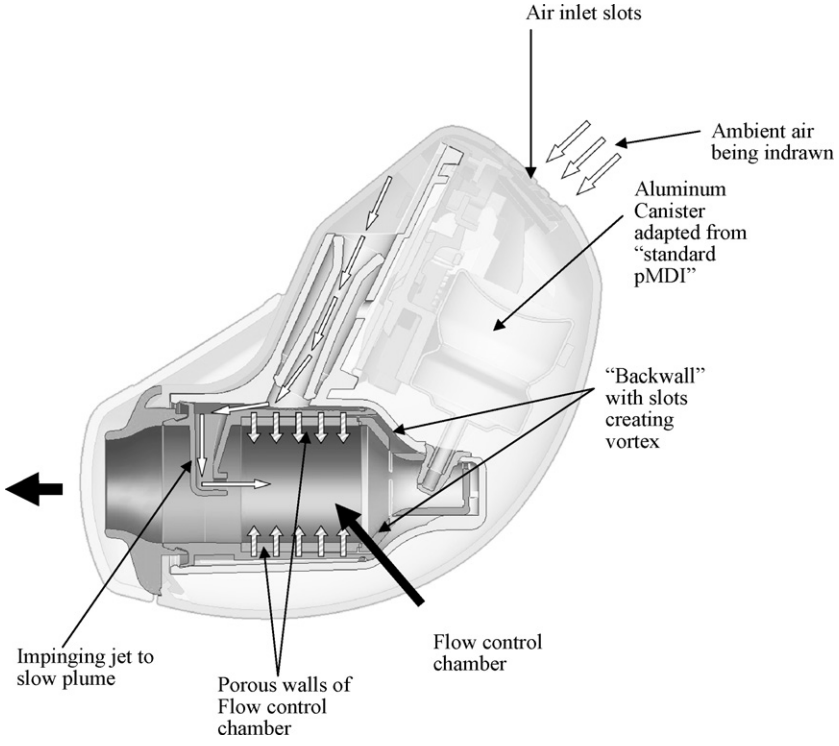

Fig. 1. Flow control chamber of the breath-synchronized, plume-control inhaler.

Twelve Tempo inhalers and three commercial inhalers, each containing FP, were evaluated at flow rates of 28.3 and 45.0 L/min. FP inhalers (Flovent®, Glaxo Wellcome Inc., Research Triangle Park, NC) containing FP 110 μg/actuation in CFC propellants were purchased from a commercial source, and their contents were radiolabeled according to methods described elsewhere (Newman et al., 2003; Snell and Ganderton, 1999). The trigger synchronous time of the Tempo inhaler was determined using an Aerobreather (Amherst Process Instrument, Inc., MA) with a limit switch controlled timer to measure the time it took to discharge FP from the Tempo inhaler at a 45.0 L/min flow rate. Data collected from the Andersen Cascade Impactor at flow rates of 28.3 and 45.0 L/m and analyzed by HPLC assay provided results for metered dose (μg), emitted dose (μg), fine particle dose (FPD, μg), fine particle fraction (FPF, expressed as % delivered dose) and non-Fine Particle Fraction (nFPF, expressed as % delivered dose). Device efficiency (FPD/metered dose, %) and device deposition (amount retained in devices (μg)/metered dose (μg), %) were calculated from collected measurements. FPF was defined as Stage 3 through the final filter for the Anderson Cascade Impactor at each flow rate.

2.2. In vivo study

The in vivo method comprised an assessment of lung deposition of ^{99m}Tc-labeled FP in healthy volunteers, using gamma scintigraphy in a randomized, two-way crossover study conducted in healthy volunteers at a single study center, Pharmaceutical Profiles, Nottingham, UK. The radiolabel (^{99m}Tc pertechnetate) was extracted from a saline solution into methyl ethyl ketone and transferred to an empty MDI canister. Contents of a fluticasone propionate MDI were cooled in liquid nitrogen and then added to the canister containing radiolabel, sealed, and sonicated for 15 min (Newman et al., 2003; Snell and Ganderton, 1999).

Preliminary in vitro work fractioned the labeled and unlabeled aerosol in an Andersen Cascade Impactor at 28.3 L/min in order to compare the particle size distribution of (1) unlabeled drug to which no radiolabel had been added; (2) labeled drug following the addition of ^{99m}Tc radiolabel; (3) the radiolabel (^{99m}Tc). Validation testing was done to document that the particle size distribution of the three aerosols was similar and that the ^{99m}Tc labeling process did not alter the particle size distribution of FP and could thus act as a valid marker in vivo for the distribution of inhaled FP aerosol, as recommended by Snell and Ganderton (1999). The total amount of ^{99m}Tc used in vivo was adjusted to allow sufficient radionuclide for good scintigraphic counts to be obtained but not to exceed 10 MBq ^{99m}Tc.

An independent ethics committee responsible for monitoring the study approved the clinical study protocol. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with United States Food and Drug Administration regulations for informed consent and protection of subject rights. Written informed consent was obtained from each subject prior to study enrollment.

Twelve healthy volunteers (male or non-pregnant, non-lactating females) aged 18–65 years, with body weight within ±25% of their ideal body weight (based on Metropolitan Life Tables, 1979) and forced expiratory volume in 1 s (FEV_1) ≥80% predicted normal were enrolled. Subjects had no history of rhinitis or atopic eczema, alcohol or drug abuse; were non-smokers (or to have quit more than 12 months previously), to have no history of serious respiratory disease (including pulmonary tuberculosis, infantile bronchiolitis, asthma), no current or recent (within 14 days) upper respiratory tract infection; no lower respiratory tract infection within 3 months; not receiving any medication that could affect airway function and not to have exceeded a predetermined prior exposure to radiation and to have normal, or if abnormal, not clinically significant, hematology and chemistry profiles and electrocardiogram (ECG) at their screening visit.

Each subject was trained to inhale at 30 L/min from both the Tempo inhaler and the commercial inhaler using placebo canisters. Subjects then received two sequential actuations of FP 110 μg from the Tempo inhaler (breath triggered by the subject) or two sequential actuations from the commercial inhaler (actuated by trained staff 1 s after onset of inhalation). After a 10 s breath hold, subjects exhaled into a filter to trap exhaled drug and radionuclide. Subjects were monitored for the next 2 h and were to return no sooner than 44 h later for dosing with the other actuator.

Gamma scintigraphy was performed to assess lung deposition immediately after dosing. Posterior and anterior images of the lungs and stomach and a lateral image of the oropharynx were recorded using a General Electric Maxicamera (GE, USA). Images of the device (actuators) and exhaled air filter were also recorded. Scintigraphic data were analyzed in accordance with the methods described by Snell and Ganderton (1999). The lung outlines from ^{81m}Kr ventilation scans were used to define the edges of the lung fields on the aerosol views. Regions of interest on the deposition images were drawn around the lungs, oropharynx, and stomach. Counts obtained were corrected for background activity, radioactive decay, and tissue attenuation (Pitcairn and Newman, 1997). In regions where anterior and posterior images were recorded, the geometric mean count was calculated prior to correction for tissue attenuation. The lung fields were divided into central, intermediate and peripheral regions, which represented large, medium, and small airways (Newman et al., 1989).

2.3. Safety/tolerability

Each subject was evaluated with periodic electrocardiograms and assessment of vital signs. Additionally each subject was questioned regarding possible adverse events at each study visit. All complaints regardless of relationship to study drug were recorded.

2.4. Statistical analysis

Descriptive statistics were provided including means and standard deviation. Between group comparisons were done

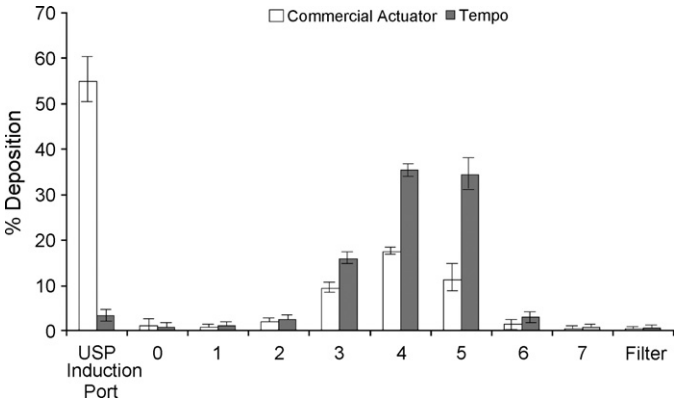

Fig. 2. Andersen cascade impactor (ACI) deposition profile ($n = 5$) highlighting differential in vitro aerosol performance between the commercial actuator and the Tempo inhaler at a flow rate of 28.3 L/min (values are mean ± standard deviation of % deposition).

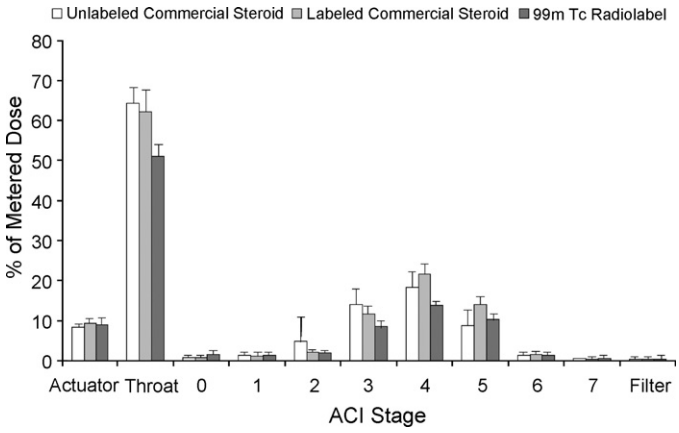

Fig. 3. Mean (±standard deviation) particle size distributions of unlabeled drug, labeled drug, and ^{99m}Tc radiolabel in the ACI operated at 28.3 L/min.

by the Wilcoxon matched-pairs signed-rank test. A significant result was considered if a p-value <0.05 was obtained.

3. Results

3.1. In vitro comparison of the Tempo inhaler and commercial inhaler

Aerosol delivery of FP from the Tempo inhaler was superior to the commercial device (Fig. 2). Fine Particle Fraction <4.7 μm was greater with the Tempo inhaler at 28.3 L/min (88.6 ± 3.6% versus 40.4 ± 4.7%) and at 45.0 L/min (89.2 ± 3.0% versus 43.1 ± 4.4%).

In vitro evaluation showed that the mean trigger time, or time to discharge FP from the inhaler, to be 0.63 ± 0.04 s at 42.5 L/min and 20 mbar for the Tempo inhaler. The mean metered dose of FP delivered via the Tempo inhaler and the commercial inhaler were comparable at 28.3 L/min and 45.0 L/min (Table 1). At each flow rate, however, the emitted dose of FP (referred to as "ex-actuator") was approximately 50% greater when delivered by the commercial inhaler compared to the Tempo inhaler. Mean FPF at a flow rate of 28.3 L/min was more than doubled for FP when delivered by the Tempo inhaler (88.6%) than by the commercial inhaler (40.4%). Similarly, mean FPF at a flow rate of 45.0 L/min was 89.2% for the Tempo inhaler and 43.1% for the commercial inhaler. Device deposition was greater on the Tempo inhaler than the commercial inhaler at both inspiratory flow rates (30.1% versus 14.6% at 28.3 L/min and 27.9% versus 13.8% at 45.0 L/min). Device efficiency was numerically higher with the Tempo inhaler than the commercial inhaler at both flow rates (54.5% versus 34.4% at 28.3 L/min and 53.9% versus 42.6% at 45.0 L/min).

3.2. In vivo deposition of inhaled ^{99m}Tc-radiolabeled FP via the Tempo inhaler and commercial inhaler

Mean (S.D.) FPF for unlabeled drug, labeled drug, and radiolabeled drug was 39.2 ± 2.9%, 39.9 ± 3.1%, and 37.1 ± 2.1%, respectively. Radiolabeling validation testing showed that the percent of metered dose was similar within the actuator, throat and all other stages for unlabeled FP, labeled FP, and labeled ^{99m}Tc (Fig. 3).

The mean age of the 12 subjects was 44.5 ± 8.0 years. Among the 12 subjects, the mean percentage of the metered dose deposited in the oropharynx was 76.8 ± 7.1% for the commercial device and 18.3 ± 7.1% ($p = 0.002$) for the Tempo inhaler, which was similar to the in vitro trend for oropharyngeal deposition (Table 2).

Drug delivery to the whole lung was significantly ($p = 0.002$) enhanced with the Tempo inhaler vs. the commercial actuator (Fig. 4 and Table 2). Regional deposition in the central, inter-

Table 1
Particle size distribution of fluticasone propionate via the Tempo inhaler and commercial inhaler

Flow rate (L/min)	Tempo inhaler		Commercial inhaler	
	28.3	45.0	28.3	45.0
Mean metered dose (μg) ± S.D.	107.1 ± 6.8	109.3 ± 6.9	123.7 ± 11.9	119.8 ± 9.6
Mean emitted dose (μg) ± S.D.	65.7 ± 5.0	69.7 ± 3.9	105.6 ± 10.4	103.3 ± 8.8
Mean FPD (μg) < 4.7 μm ± S.D.	58.3 ± 5.5	62.1 ± 4.5	42.5 ± 6.4	51.0 ± 7.0
Mean FPF (%) ± S.D.	88.6 ± 3.6	89.2 ± 3.0	40.4 ± 4.7	43.1 ± 4.4
Mean nFPF (%) ± S.D.	11.4 ± 3.6	10.8 ± 3.0	59.6 ± 4.7	56.9 ± 4.4
Device deposition (%) ± S.D.	30.1 ± 4.5	27.9 ± 5.1	14.6 ± 1.1	13.8 ± 2.7
Device deposition (μg) ± S.D.	33.1 ± 5.0	30.7 ± 5.6	16.1 ± 1.2	15.2 ± 3.0
Device efficiency (%) ± S.D.	54.5 ± 5.0	53.9 ± 4.9	34.4 ± 4.1	42.6 ± 5.2

FPD: fine particle dose, FPF: fine particle fraction, nFPF: non-fine particle fraction, device efficiency: FPD/metered dose.

Table 2
In vivo deposition of fluticasone propionate via the Tempo inhaler and the commercial inhaler ($n = 12$) as a proportion of the metered dose

Region of deposition	% ± S.D. deposition	
	Tempo inhaler FP	Commercial inhaler
Oropharyngeal	18.3 ± 7.7	76.8 ± 7.1
Whole lung	41.5 ± 9.8	13.8 ± 7.4
Central lung	11.4 ± 4.3	3.9 ± 2.9
Intermediate lung	14.8 ± 4.1	4.8 ± 2.8
Peripheral lung	15.3 ± 4.8	5.1 ± 2.6
Device	38.7 ± 9.9	8.9 ± 2.1
Exhaled air	1.5 ± 0.9	0.5 ± 0.4

mediate, and peripheral lung was also significantly ($p < 0.01$) increased compared to the commercial actuator. The mean percent deposition of FP in the whole lung region was more than three times greater when delivered with the Tempo inhaler (41.5%) than the commercial inhaler (13.8%). Dose to dose variability was reduced from 54% (commercial inhaler) to 24% (Tempo inhaler) of the delivered dose. The mean oropharyngeal:total lung deposition ratio of FP delivered by the commercial inhaler was 5.6:1 compared with 0.4:1 delivered by the Tempo inhaler. The peripheral:central deposition ratios were identical for each device (mean 1.5), highlighting that while the Tempo inhaler delivers a greater proportion of the metered dose to the lung, the distribution pattern within the lung was similar for both devices.

Typical scintigraphic images in one subject are shown in Fig. 5. Considerable oropharyngeal deposition was observed for the commercial actuator, which resulted in swallowing and transport of the inhaled dose of FP to the stomach.

3.3. Tolerability

No serious or clinically relevant adverse events were reported after inhalation of FP via either device. No adverse events were reported by 7 of 13 subjects considered in the safety analysis. Mild sore or dry throat (2), mild or moderate headache (3), and mild cold (1) were reported by one subject each.

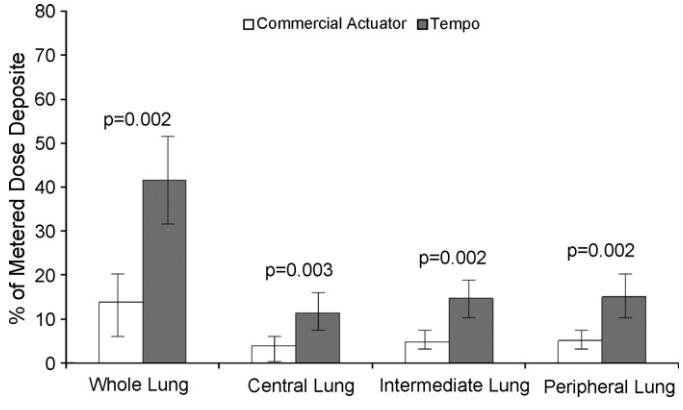

Fig. 4. Comparison of regional lung deposition (mean ± standard deviation for % of metered dose deposited) for the Tempo inhaler and the commercial actuator.

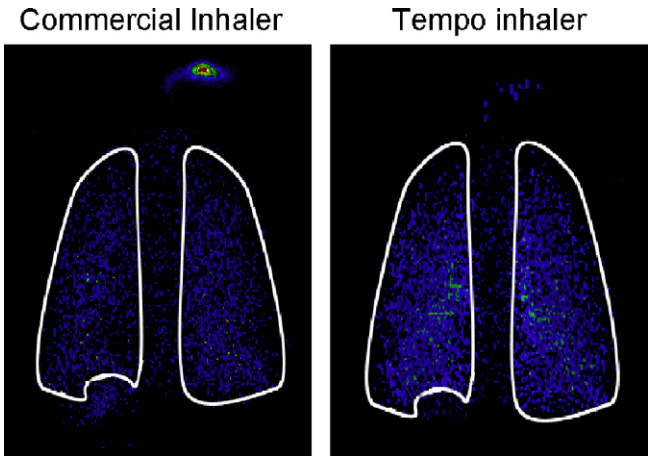

Fig. 5. Gamma scintigraphic images of fluticasone propionate distribution via the Tempo inhaler and the commercial inhaler.

4. Discussion

The results of the in vitro analysis showed that compared to the commercial inhaler, the Tempo inhaler improved efficiency of CFC-propelled FP fine particle delivery in the respirable range, increased the Fine Particle Fraction delivery, and increased the Fine Particle Dose. In vivo evaluation in healthy subjects showed that compared to the commercial inhaler, the Tempo inhaler increased whole lung, central lung, intermediate lung, and peripheral lung deliveries of FP by more than 3-fold, decreased oropharyngeal deposition by 75%, and reduced dose to dose variability from 54% to 24% of the delivered dose.

An important feature of a pMDI is the proportion of drug that actually reaches the lung versus the proportion deposited on the device and the proportion lost to oropharyngeal deposition. A wide range of lung deposition has been reported with ICS ranging from 3% up to 59% (Pauwels et al., 1997; Barnes et al., 1998; Cerasoli, 2006). The use of chlorofluorocarbon-free inhalers, spacers, and other modifications in the delivery device or drug formulation has improved lung deposition, but further improvement is needed to maximize the benefit to the patient. In contrast, oropharyngeal deposition may be as high as 80% (Roland et al., 2004), which may result in clinically significant systemic bioavailability from oropharyngeal absorption, or from gastrointestinal absorption of swallowed drug. In addition, high oropharyngeal deposition of ICS is implicated as a cause of increased local adverse effects including dysphonia, candidiasis, and local irritation, which may occur in 50% of patients (Roland et al., 2004; Derendorf et al., 2006).

It has been hypothesized that oropharyngeal deposition is the major determinant of both the magnitude of lung deposition of an inhaled aerosol, and its variability (Borgström et al., 2006). The inter-subject variability of lung deposition will tend to be high for an inhaler that gives low lung deposition and high oropharyngeal deposition. Conversely, inter-subject variability of lung deposition will tend to be low for an inhaler that gives high lung deposition and low oropharyngeal deposition. Results from this

study revealed a 3-fold higher whole lung deposition and 4-fold lower oropharyngeal deposition with the Tempo inhaler FP and a lower coefficient of variation of lung deposition (24%) compared with the commercial MDI (54%). Therefore, based on this hypothesis (Borgström et al., 2006), it would be expected that FP and potentially other drugs delivered via the Tempo inhaler would produce a more predictable and reproducible lung dose.

A number of attributes of the ideal ICS have been described, which are inherently part of the pharmacology of the drug (Cerasoli, 2006). Among these attributes, high lung deposition, low oropharyngeal deposition, and low oral or systemic bioavailability may be optimized by delivery via the Tempo inhaler because of the features of the device regardless of the specific ICS that is administered. As a result of the design of the Tempo inhaler, the discharge speed of the aerosol plume is substantially reduced, and the mean residence time is increased resulting in a higher proportion of respirable particles. Compared with a pMDI, the Tempo inhaler produces more consistent and efficient delivery of drug. Results from a study comparing the Tempo inhaler and a pMDI for delivery of ergotamine tartrate showed significantly higher systemic availability, high central to peripheral lung deposition, and low oropharyngeal deposition (Armer et al., 2007). Newman (2005) described advantages and disadvantages of the standard press-and-breathe MDI. Six disadvantages were listed: (1) the requirement for propellants, (2) difficulty in delivering high doses of drug, (3) the possibility of getting no lung delivery with poor inhaler technique, (4) drug delivery highly dependent on good inhaler technique, (5) low lung deposition and (6) high oropharyngeal deposition. The last 4 disadvantages of a pMDI can potentially be improved by the Tempo inhaler. The results of this study show that the Tempo inhaler substantially overcomes some of the disadvantages of the standard MDI.

The data from this study show that the Tempo inhaler delivers FP to the lung easily and efficiently, with lower oropharyngeal deposition and lower variability of lung dose than a standard, commercially available pMDI actuator. The Tempo inhaler may offer a better option than the traditional press and breathe pMDIs for delivery of drugs that require accurate and consistent dosing as well as drugs with high potency or a narrow therapeutic index. Specifically, the Tempo inhaler could improve ICS clinical results by reducing poorly targeted drug delivery which results in excessive long-term systemic exposure from this ineffective fraction (swallowed or impacted within the upper bronchial tree) and minimizing unwanted local exposure and the development of candidiasis and thrush in the oral cavity. Clinical trials with various drug formulations delivered by the Tempo inhaler are ongoing to confirm these findings.

Disclosure

Thomas A. Armer and Stephen B. Shrewsbury are employees of MAP Pharmaceuticals Inc., Mountain View, CA. Steven Newman and Gary Pitcairn were responsible for performing the study, which was conducted at Pharmaceutical Profiles, Ltd., Nottingham, UK under a contract with Sheffield Pharmaceuticals Inc.

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