

THE TEMPO™ INHALER – RESULTS OF PRELIMINARY TESTS IN HUMANS WITH A NOVEL PRESSURIZED METERED-DOSE INHALER (pMDI) AEROSOL DELIVERY SYSTEM

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ABSTRACT

RATIONALE: Aerosol drug delivery by pMDI remains popular but problematic. Poor coordination, wide *in vivo* variation in dose delivered, high oropharyngeal/low peripheral airway deposition limit conventional pMDIs. MAP has developed the Tempo™ Inhaler, which may overcome these limitations with a breath activated, synchronous trigger, plume control and vortexing flow control chamber system. Preliminary tests with inhaled fluticasone propionate (FP for asthma) and ergotamine tartrate (ET for migraine) compared to existing pMDIs have been conducted.

METHODS: 2 separate, crossover healthy volunteer studies: 1) ET via Ergotamine Medihaler (EM) (2052 µg) and 99mTc radiolabeled ET via Tempo (129 µg) in 12 males. 2) 99mTc radiolabeled FP via originator actuator or via Tempo in 12 subjects.

RESULTS: 1) C_{max} EM was 1019 pg/mL at 4 mins and for Tempo ET 1003 pg/mL at 3 mins. Scintigraphy with Tempo ET averaged 46% of delivered dose into lungs, coefficient of variation 25% and peripheral:central (P:C) deposition ratio 1.5 (1.0-2.3) 2) Oral deposition was 18.3% for Tempo FP, 76.8% for FP by originator actuator, and lung deposition by Tempo FP 41.5% and by originator 13.8%.

CONCLUSIONS: The Tempo system allows good targeting of peripheral airways with aerosolized drugs. This may permit predictable systemic delivery of drugs at a fraction of the delivered dose of original pMDIs, providing consistent peak systemic levels. These levels will be achieved faster than with alternative (non-IV) routes of administration but without the need for an intravenous injection. Improved lung deposition, reduced oropharyngeal deposition and less dose to dose variability may allow targeting of more potent and narrow therapeutic range drugs requiring accurate biotargeting. Tempo clinical trials are underway to further confirm these findings.

TEMPO™ INHALER BACKGROUND

Tempo is designed to significantly enhance drug delivery from pressurized metered dose inhalers (pMDIs) and consists of two lead differentiating features:

•Flow Control Chamber (Figures 1 and 2)

The *flow control chamber* manipulates the flow of the discharged plume to reduce droplet momentum and size and to match the plume velocity with the patient's inspiratory breath.

•Synchronous Trigger (Figures 3 and 4)

The *synchronous trigger* automatically discharges drug at a specific setpoint in the patient's inspiration to consistently target desired biospace.

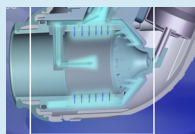


Figure 1: Air flow at start of inhalation

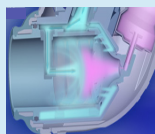


Figure 2: Plume control during pMDI discharge (immediately following synchronous trigger)



Figure 3: The airflow evacuates the diaphragm volume through the venturi siphon

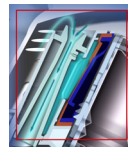


Figure 4: The diaphragm collapses, the cradle moves down discharging the canister

BACKGROUND CONTINUED

INTRODUCTION

Aerosol drug delivery by pMDI remains popular for delivery of topical anti-asthma drugs, but is more problematic when targeting drug delivery to the lungs for systemic absorption. Poor coordination, wide dose to dose *in vivo* variation in dose delivered, high oropharyngeal deposition and reduced peripheral airway deposition tend to limit the usefulness of conventional pMDIs. Migraineurs often require systemic administration when using effective ergots for headache relief. MAP has developed the Tempo inhaler, which promises to overcome these limitations with a breath synchronized plume-control inhaler (BSPCI), and is currently in clinical studies with Tempo DHE. The aim of this study (ET for migraine) was to evaluate the performance of the Tempo Inhaler (MAP Pharmaceuticals Inc., CA and Figure 5) in delivery of anti-migraine ergots.

Preliminary tests with fluticasone propionate (FP for asthma) were also conducted. The aim of this study was to evaluate the performance of the Tempo Inhaler in delivery of a commercial steroid formulation. Delivery efficiency as fine particle dose (FPD) and lung deposition of Flovent® formulation (110 mcg strength, GSK, Research Triangle Park, NC) delivered by Tempo and by the innovator's actuator were compared using *in vitro* and *in vivo* methodologies.

MATERIALS AND METHODS

ET for Migraine Study: Conducted in 2 parts: 1) A randomized, open label, two-way, cross-over trial in 12 healthy male volunteers was designed to determine the total and regional lung deposition of Tempo ET (only) and the systemic level (PK) of ET when using the Tempo device compared to Medihaler Ergotamine Tartrate (Medihaler ET) (3M, St. Paul, MN) using pharmacoscintigraphy. For PK, each volunteer received 3 administrations (2 unlabeled actuations and 1 radio labeled actuation) of ET (66 mcg metered dose/actuation, 43 mcg respirable/actuation) from the Tempo ET inhaler and 6 administrations (342 mcg/actuation) from the Medihaler ET. Subjects received both Tempo ET or Medihaler ET on one occasion each, with a four-day minimum wash-out period between study days. ET levels were assessed by gas chromatography and mass spectrophotometry, and ACI data was generated.

Part 2) A randomized, open label, two-way crossover trial in 6 healthy male volunteers to compare the systemic bioavailability of ET via 2 mg oral sublingual formulation (Lingrain®)(L) and via Tempo ET 0.258 mg dose.

MATERIALS AND METHODS

FP for Asthma Study:

In vitro Fine particle dose (FPD) was determined by measuring particle size distribution using Andersen Cascade Impactor (ACI) at 28.3 and 45 L/min for Flovent. FP mass was analyzed by HPLC. Twelve Tempo/Flovent and three Flovent/innovator samples were evaluated at both flow rates.

The Tempo trigger synchronous time was determined at the higher flow rate using an Aerobreather apparatus (Amehurst Process Instrument, Inc., MA) with a limit switch controlled timer.

In vivo Lung deposition was evaluated by gamma scintigraphy and performed at Pharmaceutical Profiles (Nottingham, UK). The study included radiolabeling Flovent with 99mTc and dosing twelve healthy volunteers using Tempo and the innovator's actuator in a randomized two-way crossover study. Validation of the Flovent radiolabel was determined using ACI at 28.3 L/min prior to dosing.

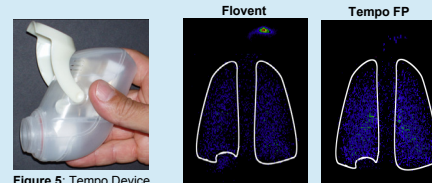


Figure 5: Tempo Device

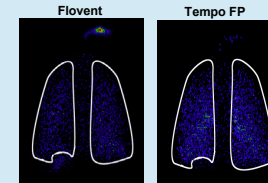


Figure 6: Scintigraphic images of Flovent and Tempo FP

RESULTS

ET for Migraine Study: Measurable amounts of ET were detectable in plasma samples from subjects receiving the 2.0 mg sublingual tablets at 1 hr post-dose, therefore concentrations of ergotamine in tablet and aerosol-treated subjects are reported in Table 1 at one min and 1 and 6 hours post-dose which were approximately 77, 8 and 2.2 times greater in plasma from Tempo treated subjects than ET levels from sublingual treatment.

Table 1: Mean and standard deviation (SD) for Ergotamine concentration (pg/mL) in subjects receiving sublingual tablet and aerosol delivery at 1 min, and 1 and 6 hr post-dose.

Treatment	1 min post-dose	1 hr post-dose	6 hr post-dose
Sublingual Tablet	27.1 (14.6) ¹	58.9 (59.7) ²	59.2 (50.8) ¹
Tempo ET (n=6)	2088.3 (1288)	492.8 (196)	129.9 (35.9)

¹ n=4 (2 BLQ) ² n=5 (1 BLQ)

The results of the lung deposition analyses are provided in Table 2, showing the percentage of metered dose delivered to the whole lung, and central, intermediate and peripheral lung regions.

The percentage deposition for lungs, oropharynx and exhalation filter were summed and expressed as percent of delivered dose and then converted to amount of drug (µg) deposited in the lung regions and the mass of drug deposited, in µg, over three actuations, based on an emitted dose of 43 µg.

RESULTS CONTINUED

FP for Asthma Study: Lung deposition of FP delivered from Tempo and from the innovator actuators is shown in scintigraphic images in Figure 6. A summary of the *in vivo* percent deposition and the indications of the extent of drug targeting in the biospace are presented in Table 2.

Table 2: Mean percentage of metered dose and standard deviation (SD) of the mass of drug (µg) deposited in lung for Tempo ET (n = 12); *In vivo* FP deposition delivered from Tempo and the innovator's standard actuator

Deposition	Oral (%)	Lung (%)	Central Lung	Intermed. Lung	Peripheral Lung	P:C Ratio
Tempo ET	40.4 (11.0)	33.5 (7.4)	8.9 (2.0)	11.4 (2.4)	13.2 (3.8)	1.5
Tempo FP	18.3 (7.7)	41.5 (9.8)				1.5
Innovator FP	76.8 (7.1)	13.8 (7.4)				1.5

*Peripheral:Central Ratio

Mean FP mass (and SD) delivered from Tempo and the innovator's actuator at 28.3 L/min and high flow are presented in Table 3.

Table 3: Mean FP dose emitted

Flow rate (L/min)	Tempo FP		Flovent	
	28.3	45	28.3	60
Metered dose (µg)	107.1 ± 6.8	109.3 ± 6.9	123.7 ± 11.9	119.8 ± 9.6
Emitted Dose (µg)	65.7 ± 5.0	69.7 ± 3.9	105.6 ± 10.4	103.3 ± 8.8
FPD (µg) <4.7 µm	58.3 ± 5.5	62.1 ± 4.5	42.5 ± 6.4	51.0 ± 7.0
FPF (%)	88.6 ± 3.6	89.2 ± 3.0	40.4 ± 4.7	43.1 ± 4.4
nRF (%)	11.4 ± 3.6	10.8 ± 3.0	59.6 ± 4.7	56.9 ± 4.4
Device Efficiency (%)	54.5 ± 5.0	53.9 ± 4.9	34.4 ± 4.1	42.6 ± 5.2
Device Deposition (%)	30.1 ± 4.5	27.9 ± 5.1	14.6 ± 1.1	13.8 ± 2.7

CONCLUSION

These results indicate that the Tempo system allows rapid systemic delivery of anti-migraine ergots at approximately 1/16th of the delivered dose of original pMDIs, providing peak systemic levels within minutes.

Tempo improved efficiency of FP particle delivery in the respirable range to 54.5% over the innovator's actuator of 34.4% at 28.3 L/min. Tempo increased FPF delivery from 40.4% to 88.6% and respirable dose from 42.5µg to 58.3µg. Tempo increased whole, central, intermediate and peripheral lung delivery 200%. Tempo reduced oropharyngeal deposition 75% and delivery variability 50%.

Tempo can deliver medications to the lung very efficiently, with lower oropharyngeal deposition and lower dose to dose variability compared to standard MDIs. Tempo has the ability to deliver formulations that have narrower therapeutic windows, require lower payloads, have higher potencies, require more biotargeting and consistent dosing with lower side effects. MAP is in clinical development with Tempo DHE for the treatment of migraine.