Using PreciseInhale for Controlled Volunteer Exposures with Aerosols Extracted from Clinical Inhalers

Per Gerde[1,2], Carl-Olof Sjöberg[1] Helen Bäckroos[1] & Helena Litorp[3,4]

[1]Inhalation Sciences AB, Hälsovägen 7, Novum, 141 57 Huddinge, Sweden. [2]IMM, Karolinska Institutet, Nobels väg 13, 171 77 Stockholm, Sweden [3]CTC Clinical Trial Consultants, Dag Hammarskjölds väg 10B, 752 37 Uppsala, Sweden
[4] Department of Global Public Health, Karolinska Institutet, 171 77 Stockholm, Sweden

Introduction

Clinical inhalers have a built-in conflict between the higher flow rate requirements to generate an optimal particle size during actuation, and to provide the usually lower flow rate suitable for the subsequent lung exposure. The PreciseInhale® (PI) clinical module therefore utilizes inhaler aerosols in two steps; 1) doses of aerosol are first actuated into an aerosol holding chamber and 2) extracted from the holding chamber for exposure at desired flow rates and inhaled volumes. Both dry powder inhalers and pressurized Metered Dose Inhalers (pMDI) can be used. Separating inhaler actuation/aspiration from drug inhalation may accomplish two improvements; I) minimize throat deposition during exposures, and II) provide for regional lung targeting using the bolus breath hold method. Both possibilities could accomplished two improvements in the use of the systemic blood concentration as a surrogate for local dose of an inhaled drug in the lungs. Firstly, minimizing throat deposition will limit the contribution from gastrointestinal absorption, and secondly, in exposures controlled by the PI, major respiratory tract regions can be selectively targeted with the bolus-breath hold method.

Two objectives were pursued; I) to compare one dose, inhaled directly form a pMDI by volunteers, with the same dose actuated and aspirated by the PreciseInhale, then inhaled using the same inhalation maneuver, and II) to compare one dose actuated and aspirated by the PI, and then inhaled as either peripheral lung boli or central airway boli.

Experimental Methods

Single doses of fluticasone propionate (FP) 250 µg and salmeterol xinafoate (SMX) 25 µg were actuated and aspirated from the pMDI Evohaler Seretide Forte (1) into the 300 mL holding chamber at a flow rate of 30 L/min for 630 ms, giving an optimal placement of aerosol in the holding chamber (Fig 1). The aerosol was then ready for a flow- and volume prompted inhalation maneuver by healthy volunteers (Fig 1B). Twelve healthy volunteers were recruited for the study. The desired breathing pattern was prompted to research subjects through a graphical interface (Fig 2). All flow rates of the dosing maneuver were monitored, together with the aerosol concentration measured with a Casella Microdust Pro instrument. The study was divided into four arms for pairwise comparison. All 12 subjects participated in each of the four study arms:

Arm 1: Direct inhalation. One dose from the inhaler was inhaled according to the label instruction. One deep breath with synchronized actuation of the inhaler at approximately 30 L/min followed by a 10 s breath hold period.

Arm 2: Whole lung. Actuation/aspiration of one inhaler dose into the PI, followed a prompted inhalation maneuver from the PI of the 300 mL aerosol volume in the beginning of a 1.5 L volume inhaled at 30 L/min, followed by a 10 s breath hold and a 1.8 L exhalation volume at 30 L/min through a PARI filter pad.

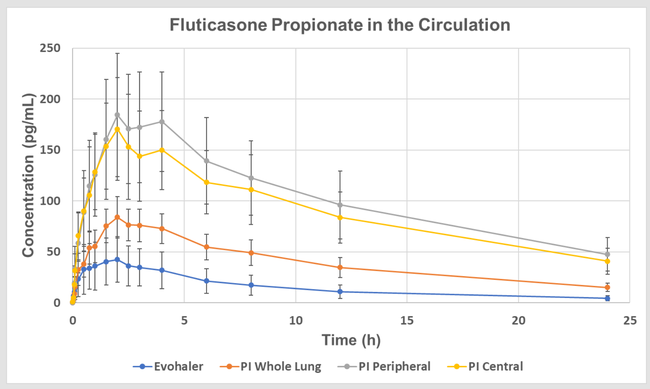
Arm 3: Peripheral lung. Actuation/aspiration of one inhaler dose into the PI, followed by the prompted inhalation of a 1 L air volume at 15 L/min with a 70 mL aerosol bolus intercalated at 500 to 570 mL followed by a 7 s breath hold and an exhalation of a 1.3 L volume at 15 L/min through a PARI filter pad. The exposure procedure was repeated 6 times in each volunteer with fresh aerosol to reach a cumulative exposure similar to the previous whole doses.

Arm 4: Central airways. Actuation/aspiration of one inhaler dose into the PI, followed by the prompted inhalation of a 1 L air volume at 15 L/min with a 70 mL aerosol bolus intercalated at 850 to 920 mL followed by a 7 s breathhold and exhalation of a 1.3 L volume at 15 L/min through a PARI filter pad. The exposure procedure was also repeated 6 times in each volunteer.

Deposition in study Arms 2-4 was determined from calculated inhaled amounts minus the amount measured on the exhalation filters. Drug deposition in filters was quantitated following dissolution in methanol and analysis using HPLC.

After each exposure procedure, blood was repeatedly sampled from an arm vein collected at 16 time points in each treatment period: pre-dose, 2, 4, 6, 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 7, 12, and 24 hours after treatment. Blood plasma samples were analyzed for both FP and SMX using LC/MS/MS (Pharm-Analyt, Baden, Austria) (Fig 3).

Study arm 1 was compared with study arm 2 to evaluate the efficiency of exposure and the precision of dosing when exposing volunteers via PI, compared to direct exposure from the inhaler. Study arm 3 was compared to study arm 4 to investigate the effect on the systemic pharmacokinetic response by placing aerosol boli of similar particle size distribution in the two major regions of the lungs at a deeper and shallower penetration depth in the lungs, respectively.



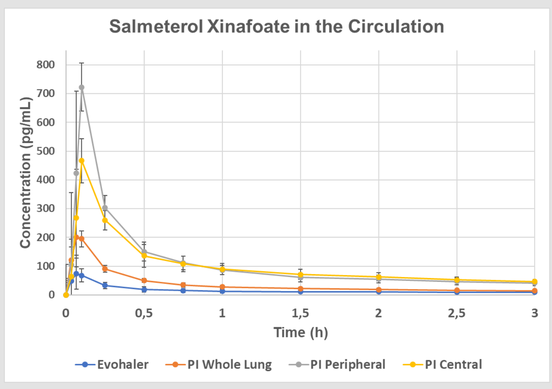
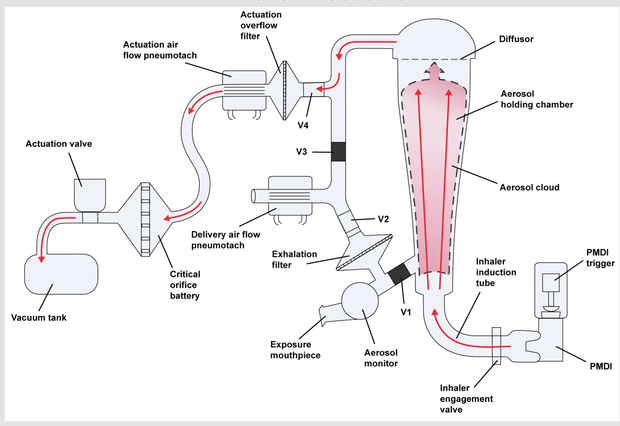


Figure 3: Concentration of FP and SMX in blood plasma following exposures under the four study arms.

Key Message

By administering clinical inhalers via PreciseInhale® an improved precision during whole lung exposures was achieved and inhaler aerosol boli could be targeted to different lung regions, which may improve *in silico* models describing the link between the elusive site-of-entry dosimetry in lungs and the measurable pharmacokinetics of the systemic circulation.



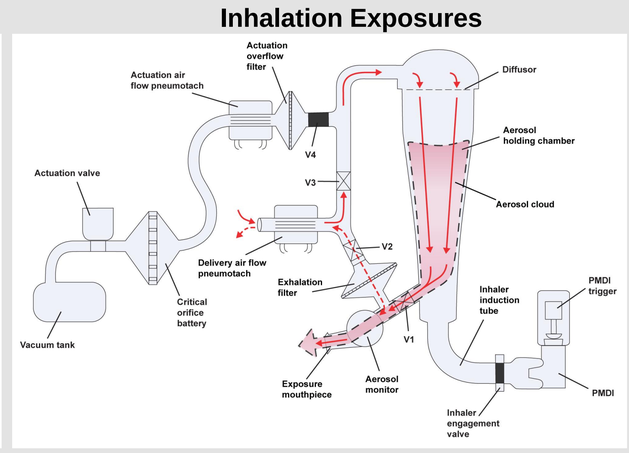
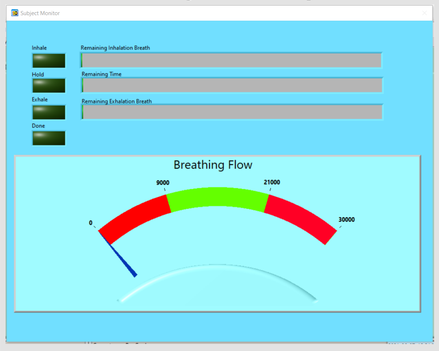


Figure 1: A) Flow scheme during actuation of the inhaler. B) Flow scheme during aerosol inhalation exposures.



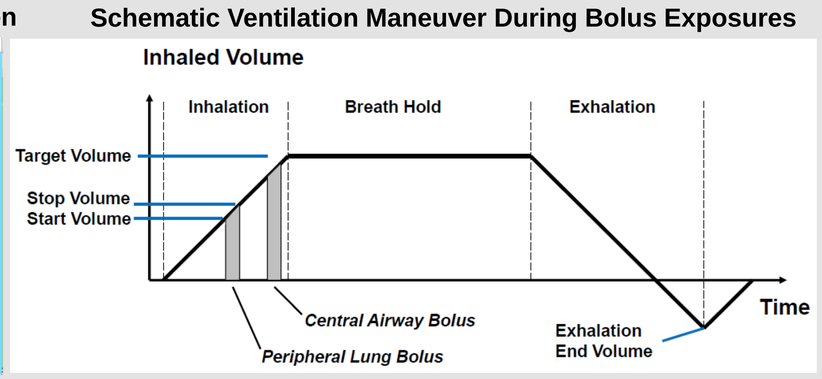


Figure 2: A) Prompter screen for reseach subjects. B) Principal ventilation scheme during bolus- breath hold exposures.

Results

By using PI for clinical exposures, the breathing pattern during the procedures can be tightly prompted and controlled for improved dosing precision and regional targeting. In case of regional targeting exposures, no direct measurement was made of bolus placement during breath hold, with for example imaging. Regional selectivity of the exposures was instead inferred from aerosol concentration measurement versus depth of penetration in the lungs and from deposition fractions of aerosol, based on measured amounts on exhalation filters. There was a clear link between the measured exhaled fraction of drugs of the PI exposures and the three different exposure procedures of Arms 2, 3 and 4 (Table 1).

For whole lung exposures, the AUC24 for SMX and FP was respectively a factor of 1.89 and 2.55 times higher for the single dose exposure administered via PI than when drawn directly from the inhaler (Table 2). This would indicate significantly lower losses when the dose was delivered via PI, compared to throat losses when the research subjects was directly inhaling the pMDI dose. Also, the average standard deviation of the AUC24 among the research subjects was lowered from ±52/56% to ±20/22% for SMX/FP when the pMDI dose was inhaled via PI compared to directly from the inhaler (Table 2).

For the bolus breath hold exposures the data indicated that the peripheral lung bolus had a higher Cmax than the central airway bolus for SMX but not for FP, even after correction for the larger deposited dose of aerosol in the peripheral lung compared to the central airways.

Study Arm	Substance	Deposited Fraction
Arm 2	FP	0.99 ± 0.01
	SMX	0.99 ± 0.00
Arm 3	FP	0.98 ± 0.01
	SMX	0.98 ± 0.01
Arm 4	FP	0.58 ± 0.15
	SMX	0.60 ± 0.16

Table 1: Fraction of inhaled aerosol deposited in the lungs during the different exposures

Inhalation Maneuver	Median Tmax (min) (Min, Max) SMX	FP	Mean Cmax (pg/ml) (±SD) SMX	FP	Mean AUC24 (h*pg/ml) (±SD) SMX	FP
Inhaler Directly	4.0 (1.8, 6.0)	120 (60, 150)	76 ± 64	46 ± 25	129 ± 67	366 ± 205
Whole Lung	4.9 (1.8, 6.0)	120 (90, 240)	213 ± 76	85 ± 20	244 ± 49	934 ± 210
Peripheral Lung	6.0 (6.0, 7.2)	150 (90, 240)	723 ± 285	195 ± 59	708 ± 192	2426 ± 728
Central Airways	6.0 (4.8, 7.2)	120 (90, 240)	290 ± 148	108 ± 51	418 ± 160	1303 ± 589

Table 2: Principal findings on the major pharmacokinetic parameters of the four study arms (N=10-12).

Conclusions

By using PI for clinical exposures, the breathing pattern during the procedures can be tightly prompted and controlled for improved dosing precision and regional targeting of the lung deposited dose in human volunteers.

The PI can be used for placing smaller volume aerosol boli at different depth of inhalation in the lung, using the bolus breath hold method. Targeting of exposures to the major respiratory tract regions can thereby be accomplished as indicated by substantially higher retained fractions of aerosol for regional exposures of the peripheral lung compared to the central airways. This may improve the understanding of the relative contribution of size-driven particle dissolution and air/blood barrier permeability to the subsequent systemic pharmacokinetic parameters of inhaled drug aerosols.

Research subjects concluded the prompted instructions on the PI patient interface to be rather easy to follow after a proper training session

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