

TITLE PAGE

Title: Effect of delivery device on systemic exposure to inhaled Fluticasone

Propionate in children with asthma

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Abbreviations: AUC = Area under the plasma drug concentration-time curve; $C_{\max}$ = maximum plasma concentration; DPI = Dry Powder Inhalator; FP = Fluticasone Propionate; pMDI = pressurized Metered Dose Inhaler; $t_{\max}$ = time to max concentration.

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MANUSCRIPT TEXT

Inhaled corticosteroids are well established as the first choice of anti-inflammatory therapy for the prophylaxis of asthma in both adults and children. Current treatment guidelines recommend that inhaled corticosteroids should be prescribed for individuals with persistent asthma at all severity levels as long-term treatment markedly reduces the frequency and severity of exacerbations. A large number of inhalation devices are used for delivery of asthma medication in children, and it is well known that choice of device is key for the amount of drug that reaches the lungs. For infants and preschool children, in whom active cooperation can be problematic, a pressurised Metered Dose Inhaler (pMDI) used in conjunction with a spacer is usually preferred for maintenance therapy whereas from ~6yrs onwards a Dry Powder Inhaler (DPI) or breath-activated MDI is recommended [1].

The switch from one delivery device to another generates a possibility of either achieving subtherapeutic drug levels or excessive drug exposure with the risk of unwanted side effects. However, there are limited childhood studies available comparing systemic exposure of inhaled corticosteroids using different inhalation devices, and thus no clear rationale for dose selection and dose titration following switch between devices in children with asthma [2].

The objective of this single-dose, randomised, double-blinded, double-dummy, crossover study was to investigate the effect of delivery device on systemic exposure to Fluticasone Propionate (FP) in children with asthma. Due to negligible oral bioavailability of FP and absence of pre-systemic metabolism in

the lung, systemic appearance of FP following inhalation is considered equivalent to lung deposition [3].

The study was conducted at the *Copenhagen Prospective Study on Asthma in Childhood* (COPSAC) clinical research unit in Copenhagen, Denmark. Children with a documented clinical history of mild asthma diagnosed according to the GINA guidelines and able to properly use the inhalation devices were included in the study. Subjects were excluded if they had changed their asthma medication, received systemic corticosteroids, had an airway infection or asthma exacerbation within 4 weeks prior to recruitment or were unable to withdraw from their controller therapy for the duration of the study.

The local Ethics Committee provided formal approval of the study (KF 02-107/98, KF 12-136/99). Written informed consent to participate in the study was obtained from subjects and their parents/guardians.

Systemic exposure to FP was examined in 13 children aged 12-15yrs (10 males), following FP 500 μ g inhaled via a DPI (Diskus®) or pMDI with spacer (Volumatic™). The FP dose delivered via pMDI plus spacer was given as two actuations of 250 μ g where each puff was inhaled with 30s of tidal breathing causing an exponential emptying of the aerosol plume. One child had parental consent withdrawn, and another child was excluded for technical reasons.

Blood samples (5mL) were collected 10min before drug administration (baseline) and 20min, 40min, 1, 2, 3, 4 and 6h post-dose for determination of FP plasma concentration [4]. The FP analysis method had a calibration range of 10-1500pg/mL from 0.5mL plasma. Mean peak inspiratory flow rate obtained during inhalation from the DPI was 107L/min (range: 45-126). Delivery of FP 500 μ g via a pMDI plus spacer compared with the DPI resulted in a 38% higher

maximal plasma concentration ($C_{\max}$) ($p=0.02$) and 70% higher area under the concentration-time curve (AUC_{last}) ($p<0.01$) (Figure 1). Time to median peak plasma FP concentration ($t_{\max}$) was furthermore longer with pMDI vs. DPI: 2h vs. 1h ($p=0.03$) (Table E1 Online).

The higher systemic exposure after pMDI plus spacer may be due to exponential emptying of the spacer following subsequent inhalations resulting in a greater inhaled volume of the aerosol and increased lung deposition compared to DPI.

With DPI, the inhaled volume of drug depends on the turbulence created by each single inhalation and increased impaction in the oropharyngeal region may be a limiting factor for lung deposition [3]. To our knowledge, no previous study has sought to titrate DPI and pMDI to deliver an equivalent lung dose in children, but results in adults have also suggested increased systemic activity with pMDI [5].

Inhaled FP follows linear pharmacokinetics in a wide dose range suggesting that the observed differences between devices will be similar for lower doses [6].

In conclusion, systemic exposure reflecting lung deposition of inhaled FP in 12-15-year-old asthmatic children was significantly higher when the dose was delivered via a pMDI plus spacer (Volumatic™) compared to DPI (Diskus®).

Therefore, we recommend that physicians and patients should be made aware that changing the device may significantly affect the lung dose, hence dose adjustment should be considered.

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FIGURE LEGENDS

Figure 1: Mean plasma concentrations of Fluticasone Propionate (FP) following administration of a single 500µg dose via Dry Powder Inhaler (DPI) (Diskus[®]) and pressurised Metered Dose Inhaler (pMDI) plus spacer (Volumatic[™]) in 12-15year-old children with mild asthma (n = 11).

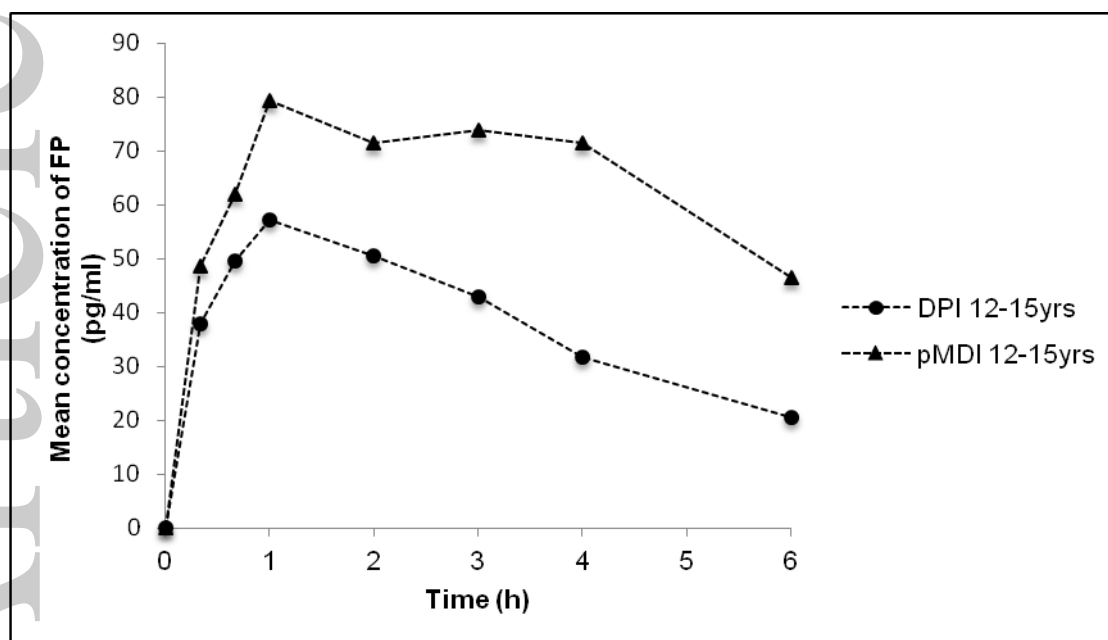


Table E1: Derived plasma pharmacokinetic parameters for Fluticasone Propionate following administration of a single 500µg dose via Dry Powder Inhaler (DPI) (Diskus®) and pressurised Metered Dose Inhaler (pMDI) plus spacer (Volumatic™) in children with mild asthma

	DPI (n = 11)	pMDI + spacer (n = 11)	% Difference	P-value
AUC _{last} (pg•h/mL) ¹	226.4 (153.5-266.2)	384.5 (288.8-465.0)	69.8	<0.01
C _{max} (pg/mL) ¹	63.7 (44.7-67.52)	87.9 (32.8-156.0)	38	0.02
t _{max} (h) ²	1.00 [0.67-3.00]	2.00 [0.67-4.00]	100	0.03

AUC_{last} = Area under the plasma concentration-time curve

C_{max} = Maximum plasma concentration

t_{max} = time to max concentration

1. Geometric LS mean (95% CI)

2. Median [range]