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Title: The fate of inhaled drug: Corticosteroid particle size effects in asthma

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Body: Background: Drug particle size influences lung deposition and systemic bioavailability of inhaled aerosols. We investigated the fate of 3 different particle sizes of inhaled fluticasone propionate (FP) in the lungs of asthmatics (AST) & healthy subjects (HS). Methods: AST (n=15, FEV_1= 81 %pred) & HS (n=15, FEV_1= 100 %pred) each inhaled 4 treatments randomised crossover; FP-50µg monodisperse particle sizes 1.5, 3, 6-µm and FP-250µg pMDI. FP plasma concentrations were quantified from baseline to 12-h post-dose. Results: Smaller FP particles (1.5, 3-µm) achieved significantly ($p<0.05$) higher peak concentrations (C_{max}) and showed greater airway clearance and systemic absorptive bioavailability (AUC_{0-12h}) compared to larger particles (6µm) and pMDI, in both AST & HS [C_{max} (AST:HS pg/mL) 1.5µm(425:359), 3µm(278:290), 6µm(85:63), pMDI(52:65); $AUC_{(0-12h)}$ (AST:HS pg.h/mL) 1.5µm(923:723), 3µm(891:933), 6µm(222:204), pMDI(182:199)]. In both AST & HS, 1.5µm FP particles showed faster clearance from the plasma compartment compared to other particles, and final 12-h concentrations were similar for all 4 treatments. We previously showed 1.5µm monodisperse aerosols achieve greater total lung and distal airways deposition compared to 6µm particles. Conclusions: The systemic bioavailability of inhaled FP is related to its drug particle size, and may be a function of total lung dose and regional airways deposition. Striking differences in the behaviour of different sized drug particles exist within the airways and can be investigated using pharmacokinetics. Each drug formulation interacts differently with the many airways factors that influence and govern the ultimate fate of inhaled drug transport within and beyond the lungs.