Urinary Pharmacokinetic Methodology To Determine The Relative Lung Bioavailability Of Inhaled Corticosteroids

Urinary pharmacokinetic methods have been introduced to identify the relative lung and systemic availability of inhaled drugs but have not been extended to corticosteroids. The main aims were to validate the urinary pharmacokinetic methodology when applied to inhaled beclometasone dipropionate (BDP), demonstrate the usefulness of the method and compare its indices to the *in-vitro* characteristics of the emitted dose.

A simple and sensitive LC-MS method for quantifying BDP and its metabolites in methanol (for *in-vitro* studies) and urine samples was identified and validated in accordance with the FDA and ICH guidelines. The accuracy, precision, and recovery of the method were within acceptable limits (±15%).

Twelve healthy volunteers completed the *in-vivo* urinary pharmacokinetic validation of the methodology to determine the relative lung bioavailability of inhaled beclometasone following inhalation. Twelve healthy volunteers received randomised doses, separated by >7 days, of 2000μg BDP solution with (OralC) and without (Oral) 5g oral charcoal, ten 100μg inhalations from a Qvar® Easi breathe metered dose inhaler (pMDI) with (QvarC) and without (Qvar) oral charcoal and eight 250μg inhalations from a Clenil® pMDI (Clenil). Subjects provided urine samples at 0, 0.5, 1, 2, 3, 5, 8, 12, and 24 hours post study dose. Urinary concentrations of BDP and its metabolites, 17-beclometasone monopropionate (BMP) and beclometasone (BOH) were measured. No BDP, BMP, or BOH was detected in any samples post OralC dosing. Post oral dosing, no BDP was detected in any of the urine samples and no BMP or BOH was excreted in the first 30 minutes. Significantly more ($p<0.001$) BDP, BMP and BOH was excreted in the first 30 minutes and cumulative 24 urinary excretions post Qvar and Clenil compared to Oral. Using 30 minute urinary excretion the mean ratio (90% confidence interval) for Qvar compared to Clenil was 231.4 (209.6, 255.7). The results confirm that the relative lung and systemic bioavailability can be identified from urinary excretion of BDP and its metabolites over the first 30 minutes and 24 hours respectively. The 2-fold difference between Qvar and Clenil is consistent with related clinical and pharmacokinetic studies. The low inter and intra-subject variability of the study confirms the reproducibility of this method. When compared to the in-vitro aerodynamics characteristics of the emitted dose, using standard compendial methods, the in-vivo indices showed a relationship to the fine particle dose (FPD) and the emitted dose (ED), respectively.

The application of this urinary pharmacokinetic method was demonstrated in further studies to compare the effect of different spacers and different washing methods on the *in-vivo* drug delivery post inhalation from Clenil and Qvar inhalers in healthy volunteers. In addition, the in-vitro aerodynamic particle size distribution of the same inhalation methods has been investigated using the Andersen Cascade Impactor according to the standard compendial methodology. Urinary excretion, using 24 hour excretion, revealed that relative bioavailability to the body was reduced with spacers for both inhalers. There was no increase in the relative lung bioavailability when Qvar was used with spacers. When Clenil was attached to a spacer (either AeroChamber or Volumatic) the relative lung bioavailability was significantly greater only if the spacers were not rinsed after washing with detergents. Consistent with the above study there were correlations between the in-vivo urinary indices and the in-vitro characteristics of the emitted dose.

The thesis highlights the extension of the urinary pharmacokinetic method to inhaled beclometasone dipropionate and provides further evidence of *in-vitro in-vivo*

correlations between the urinary methodology and the aerodynamic characteristics of the emitted dose.
Keys words: beclometasone dipropionate, metabolites, urinary excretion, metered dose inhalers, spacers, relative lung bioavailability, and in-vitro dose emission.