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The systemic exposure to inhaled beclometasone/formoterol pMDI with valved holding chamber is independent of age and body size

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ABSTRACT

Background: Asthma guidelines recommend prescription of inhaled corticosteroids at a reduced dosage in children compared to older patients in order to minimize the systemic exposure and risk of unwanted side effects. In children, pressurized metered dose inhalers (pMDI) are recommended in combination with a valved holding chamber (VHC) to overcome the problem of coordinating inhalation with actuation. However, the influence of age and body size on the systemic exposure of drugs to be administered *via* a pMDI with VHC is still not fully elucidated. Therefore, we aimed to compare the systemic exposure to the active ingredients of a fixed combination of beclometasone-dipropionate/formoterol-fumarate administered *via* pMDI with VHC in children, adolescents and adults.

Methods: The pharmacokinetics of formoterol and beclometasone-17-monopropionate (active metabolite of beclometasone-dipropionate) was evaluated over 8 h from three studies, each performed in a different age and body size group. Children (7–11 years, $n = 20$), adolescents (12–17 years, $n = 29$) and adults (≥18 years, $n = 24$) received a single dose of beclometasone/formoterol (children: 200 μg/24 μg, adolescents and adults: 400 μg/24 μg) *via* pMDI with AeroChamber Plus™.

Results: The systemic exposure in children in comparison to adolescents was equivalent for formoterol while it was halved for beclometasone-17-monopropionate in accordance with the halved dose of beclometasone administered in children (90% CIs within 0.8–1.25 for formoterol and 0.4–0.625 for beclometasone-17-monopropionate). The systemic exposure to beclometasone-17-monopropionate and formoterol was equivalent between adolescents and adults.

Conclusions: The systemic exposure to the active ingredients of a fixed dose combination of beclometasone/formoterol administered *via* pMDI with AeroChamber Plus™ correlates with the nominal dose independently of patient age and body size. Thus, dose reduction in relation to age when using a pMDI with VHC may be unnecessary for reducing the systemic exposure in children.

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1. Introduction

International guidelines for treatment of childhood asthma such as GINA [1] recommend prescription of inhaled corticosteroids adjusted to age or body size [2–5]. The deposition of drug in the lungs determines the clinical response, whereas systemic exposure in terms of drug concentration in the bloodstream determines the risk of systemic side effects. Children in comparison to adolescents and adults under the same anti-asthmatics dose regimen may be exposed to significantly higher systemic concentrations due to their

Abbreviations: AUC, area under the plasma drug concentration-time curve; BDP, beclometasone-dipropionate; B17MP, beclometasone-17-monopropionate; C_{max}, maximum plasma concentration; FEV_1, forced expiratory volume in 1 s; FF, formoterol-fumarate; ICS, inhaled corticosteroids; PK, pharmacokinetics; pMDI, pressurized metered dose inhaler; $t_{1/2}$, half-life; t_{max}, time to maximum plasma concentration; VHC, valved holding chamber.

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lower body size. Thus, the rationale behind age and body size dose adjustment is to reduce the systemic exposure and minimize the risk of unwanted side effects in children. However, the influence of age and body size on the systemic exposure is not yet fully elucidated.

An extra-fine hydrofluoroalkane (HFA) fixed pressurized metered-dose inhaler (pMDI) combination of beclometasone dipropionate (BDP)/formoterol fumarate (FF) is licensed for use in asthmatic adults and currently under development in the pediatric population. In children, pMDIs are recommended to be used in combination with valved holding chambers (VHCs) to avoid the problem of coordinating inspiration with actuation. VHCs maximize lung deposition and minimize the extra-thoracic delivery of drug. In a recent scintigraphic study [6] in which a FF pMDI formulation [7] with the same composition of BDP/FF pMDI [8] was used in conjunction with AeroChamber Plus™, the extra-thoracic drug delivery was minimized to less than 10% of the total nominal dose. Considering that only a fraction (oral systemic availability [6,9,10]) of the extra-thoracic component contributes to the total blood levels, the systemic exposure to beclometasone-17-monopropionate (B17MP; active metabolite of BDP) and formoterol after inhalation *via* BDP/FF pMDI with AeroChamber Plus™ can be considered a reasonable indicator of lung deposition.

Debate remains regarding the safety of long-term use of inhaled corticosteroids/long acting β_2-agonists (ICS/LABA) in children [11–13]. Concerns primarily arose from short-term studies showing reduced lower leg growth rate and impact on the hypothalamic-pituitary-adrenal axis after using ICS [14]. The clinical relevance of these findings is still unknown, but a recent large randomized controlled study of 943 children with asthma demonstrated a lower mean adult height of 1.2 cm in the budesonide treated children compared to placebo [15]. Therefore, prescription of ICS to children have been recommended at lower nominal doses of that recommended in adults [1,2,4].

In a previous study we found similar systemic exposure to a fixed nominal dose of budesonide delivered *via* a pMDI with VHC in children and adults [16]. This suggests that dose-reduction in relation to age may lead to significantly lower systemic exposures in young patients, possibly reflecting a lower and sub-therapeutic lung dose. In the present study, we have again investigated the influence of age and body size on the systemic exposure from an ICS/LABA fixed combination inhaled *via* pMDI with VHC. We studied the systemic exposures to formoterol and B17MP after a single dose administration of BDP/FF pMDI used with AeroChamber Plus™. In order to disentangle the effects of age and body size, we studied three different asthma populations: (1) children aged 7–11 years, (2) adolescents aged 12–17 years, and (3) adults aged ≥18 years.

2. Materials and methods

2.1. In vitro study data

An Andersen Cascade Impactor (ACI) (Copley Instruments, Nottingham, UK) operated at 28.3 l/min was used to determine the particle size distributions of the pMDI with VHC used in the study at two different dose strengths of BDP/FF (100/6 μg and 50/6 μg per actuation). Devices were actuated directly into the induction port of the impactor and the amount of drug collected at each stage was determined using a high performance liquid chromatography with U.V. detector fully validated method. The delivered dose was the amount of drug deposited in the induction port as well as in all stages of the impactor (S0-Filter). The total emitted dose was the delivered dose plus the amount of drug recovered in the actuator and spacer. The fine particle dose (ACI stages S3-Filter; particles <4.7 μm), the fine particle fraction (fine particle dose expressed as % of the delivered dose), the coarse dose (induction port plus ACI stages S0–S2; particles >4.7 μm), the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were also evaluated.

2.2. Patients

Study data was collected from three independent clinical trials each performed on a different age group population, namely children (7–11 years) [ClinicalTrials.gov ID: NCT01848769] [17] adolescents (12–17 years) [ClinicalTrials.gov ID: NCT01803087] and adults (≥18 years) [ClinicalTrials.gov ID: NCT01349257]. Patients with a documented clinical history of asthma diagnosed by the responsible physician of each trial according to the GINA guidelines [1] and under regular treatment with ICS or ICS/LABA or using short-acting inhaled β_2-agonist as reliever to control asthma symptoms, were considered for inclusion in the study. Eligible patients were all those able to properly use a pMDI with VHC and with a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) >70% (≥60% for adults) of predicted values (% pred). Main exclusion criteria were exacerbation of asthma symptoms or lower respiratory tract infection within the previous 4 weeks and past or present diagnoses of cardiovascular, renal or liver disease.

2.3. Ethics

Trials were conducted in accordance with the Declaration of Helsinki (1996) and written informed consent was obtained from all patients.

The trial in children (EudraCT 2009-010434-22) was approved by the Danish Medicines Agency; approval number 2612-4085 on the 13 August 2009 and by The Health Secretariat, The Research Ethics Committees for the Region Midtjylland; Approval number 20090106.

The trial in adolescents (EudraCT 2011-005108-14) was approved by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products 41 zabkowska str. 03-736 Warsaw; approval: ur.dbl.ble.4500.430.2011 dated 30 Jan 2012 and by the Bioethics Committee at the Medical University in Lodz 4 kosciuszki av., 90-419 Lodz approval: rnn/221/11/ke dated 13 December 2011.

The trial in adults (EudraCT 2010-024384-40) was approved by the NRES – Committee North West – Greater Manchester Central M1 3DZ – Manchester–UK Approval: 11/NW/0160 15 Apr 2011 and by the MHRA Approval: 06607/0243/001-0001 28 Apr 2011.

2.4. Study design

Each age group population was dosed with a HFA-propelled extra-fine fixed combination of BDP/FF pMDI (Chiesi Farmaceutici, Parma, Italy) in combination with AeroChamber Plus™ (Trudell Medical International, Ontario, Canada) in one of the treatment periods. In the present study the pharmacokinetic (PK) profiles of formoterol and B17MP in adults, adolescents and children obtained after administration of 4 puffs of BDP/FF pMDI with AeroChamber Plus™ was studied. In adults and adolescents each actuation contained 100/6 μg (BDP/FF), giving a total dose of 400/24 μg. In children the BDP/FF dose was 50/6 μg per actuation, giving a total dose of 200/24 μg. pMDIs were primed prior to administration and the AeroChamber Plus™ were cleaned in accordance with the instructions leaflet. The use of short acting β_2-agonists, LABA and BDP, had to be avoided for at least 4, 24 and 48 h, respectively, prior to study drug administration. At the end of inhalation treatment, adult patients were given orally 5 g of activated charcoal suspended in

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