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Systemic exposure to inhaled beclometasone/formoterol DPI is age and body size dependent

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Summary

Aim: Prescription of inhaled corticosteroids to children with asthma is recommended at half the nominal dose of adults in order to reduce the risk of systemic side effects. However, there is a lack of pharmacokinetic trials supporting such dose reduction regimens. Therefore, we aimed to compare the systemic exposure to the active ingredients of a fixed dose combination of beclometasone-dipropionate (BDP) and formoterol after dry powder inhaler (DPI) administration in children, adolescents and adults.

Methods: The pharmacokinetic profiles of formoterol and beclometasone-17-monopropionate (B17MP; active metabolite of BDP) were evaluated over 8 h from two independent studies comprising children (6—11yrs, $n = 27$), adolescents (12—17 yrs, $n = 28$) and adults ($\geq$18 yrs, $n = 30$) receiving a single, fixed dose of BDP/formoterol (children: 200 μg/24 μg, adolescents and adults: 400 μg/24 μg) via DPI.

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Results: The systemic exposure (AUC) for children versus adults was almost doubled for formoterol and similar for B17MP despite the halved BDP dose administered in children. In adolescents the AUC for formoterol and B17MP were approximately one third higher than in adults for both compounds. Upon normalization for the BDP/formoterol dose in the three populations the AUC and peak concentration (C_{max}) correlated inversely with age and body surface area of the patients ($r \leq -0.53$; $p < 0.0001$).

Conclusion: The systemic exposure to the active ingredients of BDP/formoterol administered as DPI correlates inversely with age and body size suggesting that dry powder dosage regimens should be adjusted for age and body size to avoid high systemic drug levels in children.

What this paper adds

What is already known about this subject

Clinical guidelines for treatment of children with asthma recommend dosing of inhaled corticosteroids adjusted to age or body size. However, the influence of age and anthropometrics on the systemic exposure of drugs inhaled as a dry powder formulation is poorly elucidated.

What this study adds

This study documents that the systemic exposure from a fixed dose of beclometasone-dipropionate/formoterol DPI correlates inversely with age and body surface area resulting in increased blood levels in younger patients. The findings support guideline recommendations of a reduced dosage regimen of dry powder formulations in children in order to avoid systemic side effects such as growth retardation.

Introduction

Asthma guidelines recommend prescription of inhaled corticosteroid (ICS) to children adjusted according to age and body size. Thus, ICS dosage to children is recommended in half the nominal dose of that recommended in adults [1–3]. The rationale behind dose reduction in children is based on a concern for systemic side effects such as impaired growth rate [4] and reduced adult height [5]. However, the influence of age and body size on the proportion of an inhaled drug dose that reaches the systemic circulation, i.e. the systemic exposure, is poorly understood.

In two previous studies comparing the systemic exposure to a fixed nominal dose of budesonide pressurized metered dose inhaler (pMDI) inhaled from a spacer (Nebuchamber) in children and adults [6] and a fixed nominal dose of beclometasone-dipropionate (BDP)/formoterol combination pMDI inhaled from the AeroChamber Plus™ spacer device in children, adolescents and adults [7] we found comparable levels of ICS and long acting β_2-agonists (LABA) in the bloodstream independently of age and body size. This suggests that the current praxis of dose reduction in children to avoid high systemic exposure may be unnecessary when prescribing ICS pMDI with a spacer.

The purpose of the current work was to investigate if systemic exposure to ICS is also independent of age and body size when inhaled from a dry powder inhaler (DPI).

Therefore, we compared the pharmacokinetic profiles after a single dose administration of BDP/formoterol combination DPI in children, adolescents and adults with asthma.

Methods

Patients

Study data was collected from two independent clinical trials, one performed on children (6–11 yrs) [ClinicalTrials.gov Identifier: NCT01468272]. Identifier: NCT01468272] and one on adolescents (12–17 yrs) and adults (≥18 yrs) [ClinicalTrials.gov Identifier: 108 NCT01191424]. Identifier: NCT01191424]. Children, adolescents and adults with a documented clinical history of asthma diagnosed according to the GINA guidelines [8] and under regular treatment with ICS or ICS/LABA or using short-acting inhaled β_2-agonist as reliever therapy to control asthma symptoms were considered for inclusion in the study. Eligible patients were those able to properly use a DPI and with a pre-bronchodilator Forced Expiratory Volume in one second (FEV_1) >70% of predicted values [9]. Main exclusion criteria were exacerbation of asthma symptoms or lower respiratory tract infection within the previous 4 weeks and past or present cardiovascular, renal or liver disease. The clinical trials were carried out in accordance with the Declaration of Helsinki (1996), the ICH

Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and with applicable regulatory requirements. Protocols were approved by Independent Ethics Committee. Written informed consent was obtained from the parents/guardians at the screening visit.

Study design

Each age group population was treated according to an open label, randomized, single dose, two-way crossover design in which asthmatic patients were dosed with the fixed combination BDP/formoterol DPI (NEXThaler®, Chiesi Farmaceutici, Parma, Italy) in one treatment period and with the equivalent nominal dose of BDP DPI and formoterol DPI given separately in another treatment period. A washout period of at least 7 days separated each drug administration. In the present study the pharmacokinetic (PK) profiles of formoterol and beclometasone-17-monopropionate (B17MP, active metabolite of BDP) obtained after treatment with the fixed BDP/formoterol combination DPI were compared between the different age group populations.

A screening visit including medical history, physical examination, and lung function assessment was performed within 30 days before the first drug administration. At this screening visit and prior to the study drug administrations, patients practiced the inhalations with placebo DPI until the investigator judged the technique to be optimal. The patients were instructed to hold their breath for as long as possible (>5 s) following each inhalation and to wait about 30 s before taking the next inhalation.

Prior to each study drug administration, intake of short acting β_2-agonists, LABA and BDP had to be avoided for at least 4, 24 and 48 h, respectively. The study drug was a dry powder fixed combination of BDP 100 μg and formoterol 6 μg per actuation (BDP/formoterol 100/6 DPI) for adults and adolescents and BDP/formoterol 50/6 DPI for children. Patients were dosed with 4 inhalations of BDP/formoterol DPI for a total dose of 400 μg/24 μg in adults and adolescents and 200 μg/24 μg in children. The dosage corresponded to the total allowed daily dose in order to properly assess the plasma profile of the analytes also during the elimination phase taking into account that especially formoterol plasma levels are very low even at the maximum daily dosage of 24 μg.

Evaluable patients in this study were all those receiving BDP/formoterol DPI excluding subjects without any valid PK measurement over 8 h post-dose or with major protocol deviations significantly affecting the pharmacokinetics such as incorrect inhalation, change in patient condition (e.g. worsening of asthma, cold), failure in delivery of the device, use of non-permitted medications. Study patients were not excluded on the basis of statistical analysis or for PK reasons.

Pharmacokinetic assessments

Patients attended the clinics in the morning of the administration day after having fasted overnight and remained fasted until 2 h post-dosing. They remained seated as much as possible, avoided strenuous activities, and remained under constant surveillance of the nursing staff. No alcohol or xanthine containing beverages or foods (tea, chocolate, cola, etc.) or grapefruits were allowed from 48 h before each drug administration until 24 h after administration. No food or drink, except water, was allowed for 2 h after drug administration.

Prior to study drug administration, an intravenous cannula was inserted into a cubital vein anesthetized with Lidocain gel (EMLA®) for collection of blood samples.

The administration of the study drug was made in a dedicated room well separated from the blood sampling station and the on-site laboratory to avoid any risk of contamination.

Blood samples were collected pre-dose and at 0.25, 0.5, 1, 2, 4, 6, 8 h post-dose. Blood samples for B17MP and formoterol determination in plasma were collected into vacuum tubes containing EDTA and lithium heparin, respectively. All samples were immediately chilled on ice bath and plasma preparation was done within 15 min after blood collection. The plasma was separated in a refrigerated centrifuge at +4 °C and at 2500 rpm for 15 min and subsequently transferred into prelabelled polypropylene tubes. For stabilizing the formoterol compound, the polypropylene tubes were pre-filled with 50 μL of citric acid and centrifuged before use in order to ensure that the citric acid was at the bottom of each tube. Samples for B17MP and formoterol analysis were stored below −20 °C and −65 °C, respectively, before shipment on cold dry ice to the laboratory (SGS Life Sciences Services, Belgium). The PK assays were performed using validated liquid chromatography-mass spectrometry (LC-MS/MS) methods with lower limit of quantification of 2 pg/ml for formoterol and 50 pg/ml for B17MP [10].

The following PK parameters were calculated from the individual plasma drug concentration vs. time profiles: maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), area under the plasma concentration−time curve observed from 0 to 8 h post dose and to infinity (AUC_{0-t}, $AUC_{0-\infty}$, respectively) and half-life ($t_{1/2}$) calculated as $0.693/\lambda z$, where λz is the first order terminal rate constant.

Data analyses

PK study calculations and statistical comparisons of PK data were performed according to a noncompartmental kinetic model using Phoenix™ WinNonlin® version 6.2.1 (Pharsight Corporation, USA). AUC was calculated using the linear trapezoidal rule. We tested age dependency of AUC and AUC normalized for the body surface area (BSA) as AUC × BSA where BSA was calculated according to the Mosteller formula [11]. All PK variables were log transformed and analyzed with an analysis of variance (ANOVA) model. The 90% confidence intervals (CIs) for the ratio of the geometric means were derived from the model. Equivalence was demonstrated if the 90% CI range was within the 0.8−1.25 acceptance region [12]. Statistical comparisons of demography data and correlation assessments were performed by means of one-way ANOVA followed by post-hoc Dunnett's test for multiple comparisons and Spearman's non-parametric test, respectively, using

GraphPad Prism® version 6.0 (GraphPad Software, Inc, USA). Differences and correlations were considered significant at $p <0.05$.

Results

Study population

Twenty-seven patients were enrolled in the children trial. One child was withdrawn after treatment leaving 26 children evaluable for this study (6 aged 6–8 yrs and 20 aged 9–11 yrs). 18 were males (69%) and 8 were females (31%) with an overall mean age of 9.3 yrs (range 6–11). One out of the 26 evaluable patients was excluded from the PK analysis of B17MP due to a missing plasma concentration 8 h post-dose.

Twenty-eight patients were enrolled in the adolescent trial and all of them were evaluable for this study. 15 were males (54%) and 13 were females (46%) with an overall mean age of 13.9 yrs (range 12–17).

Thirty patients were enrolled in the adult trial and all of them were evaluable for this study. 17 were males (57%) and 13 females (43%) with an overall mean age of 35.1 yrs (range 19–59). Two out of the 30 evaluable patients were excluded from the PK analysis of B17MP due to missing plasma concentrations 8 h post-dose.

In the three age group populations BSA increased significantly from children to adolescents and from adolescents to adults ($p < 0.001$) (Online Fig. E1). The mean BSA was 1.15 m^2 (range 0.78–1.46) for children, 1.56 m^2 (range 1.23–1.86) for adolescents and 1.90 m^2 (range 1.49–2.19) for adults.

The study population demography data are outlined in Table 1.

Pharmacokinetics

The overall summary of PK parameters and the mean plasma concentration–time profiles over the 8 h sampling period are represented in Table 2 and Figs. 1 and 2. The systemic exposures were higher in adolescents as compared to adults for both B17MP and formoterol. The point estimates (PE) and 90% CI of the geometric means ratio adolescents/adults for AUC$_{0-t}$ was 1.42 (90% CI, 1.28–1.57) for B17MP and 1.20 (90% CI, 1.08–1.35) for formoterol (Table 3). Similarly to the systemic exposure, C_{max} was higher in adolescents as compared to adults for both B17MP (PE,

1.68; 90% CI, 1.50–1.89) and formoterol (PE, 1.27; 90% CI, 1.11–1.44) (Table 3). Upon normalization for BSA of each individual patient, the systemic exposure was equivalent for adolescent and adults. In fact, the 90% CI of the geometric means ratio adolescents/adults for the variables AUC$_{0-t}$ × BSA and AUC$_{0-inf}$ × BSA were completely within the bioequivalence reference intervals of 0.8–1.25 [12] with the only exception for AUC$_{0-t}$ of B17M with the upper 90% CI of 1.27 being slightly above the upper reference level (Table 3).

Children in comparison to adults were treated with a halved dose of BDP (200 μg vs. 400 μg) but with the same dose of formoterol (24 μg). Despite a halved BDP dose in children, the systemic exposures in children and adults were comparable for B17MP, while it was higher in children for formoterol (Table 3). The PE of the geometric means ratios children/adults for AUC$_{0-t}$ was 0.90 (90% CI, 0.81–1.00) for B17MP, and 1.85 (90% CI, 1.64–2.07) for formoterol (Table 3). Similarly, the PE for C_{max} was 1.23 (90% CI, 1.09–1.39) for B17MP and 1.86 (90% CI, 1.62–2.13) for formoterol (Table 3). Upon normalization for BSA, the systemic exposure of children in comparison to adults was halved for B17MP (according with the halved dose of BDP) and equivalent for formoterol: the 90%CI of AUC × BSA was within the range 0.40–0.625 for B17MP and within the bioequivalence range of 0.80–1.25 for formoterol (Table 3).

The terminal half-lives ($t_{1/2}$) for both B17MP and formoterol were similar among the three age group populations. Mean (SD) $t_{1/2}$ for children, adolescents, and adults were: 2.6 ± 0.7 h, 2.6 ± 0.6 h and 3.5 ± 0.7 h for B17MP and 3.6 ± 0.7 h, 4.0 ± 0.9 h and 4.7 ± 1.7 h for formoterol, respectively.

Upon normalization for the BDP/formoterol dose in the three age group populations (normalization of the BDP component in children to 400 μg), the systemic exposure and peak concentration to B17MP and formoterol expressed as AUC$_{0-t}$ and C_{max} correlated inversely with the BSA ($r \leq -0.71$; $p < 0.0001$) and age ($r \leq -0.53$; $p < 0.0001$) of the patients (Figs. 3 and 4).

Discussion

Main finding

The systemic exposure to the active metabolite of BDP (B17MP) and formoterol after dry powder inhalation

Table 1 Study group demography.

	Children ($N = 26$)	Adolescents ($N = 28$)	Adults ($N = 30$)
Age (years)	9.3 (1.5; 6–11)	13.9 (1.7; 12–17)	35.1 (10.4; 19–59)
Weight (kg)	34 (8; 19–52)	54 (9; 38–71)	75 (12; 50–97)
Height (cm)	139 (11; 116–157)	162 (10; 142–181)	174 (9; 151–192)
BMI (kg/m^2)	17.5 (2.3; 14.1–24.0)	20.4 (1.9; 18.6–26.5)	25.0 (2.9; 19.9–30.7)
BSA (m^2)	1.15 (0.17; 0.78–1.46)	1.56 (0.18; 1.23–1.86)	1.90 (0.19; 1.49–2.19)
FEV$_1$ (L)	1.81 (0.42; 1.01–2.69)	3.01 (0.65; 1.91–4.52)	3.56 (0.87; 2.25–5.46)
FEV$_1$ %pred (%)	91 (13; 72–111)	105 (15; 77–142)	97 (14; 77–118)

Results are presented as the mean (SD; range). BMI: body mass index; BSA: body surface area calculated according to the Mosteller formula; FEV$_1$: pre-bronchodilator forced expiratory volume in 1 s; FEV$_1$ % pred: FEV$_1$ % of predicted normal value.

Table 2 Beclometasone 17-monopropionate (B17MP) and formoterol pharmacokinetic parameters in children, adolescents and adults.

	AUC_{0-t} (pg*h/mL) Mean (SD)	AUC_{0-inf} (pg*h/mL) Mean (SD)	C_{max} (pg/mL) Mean (SD)	t_{max} (h) Median (range)	$t_{1/2}$ (h) Mean (SD)	$AUC_{0-t} \times BSA$ (pg*h*m^2/mL) Mean (SD)	$AUC_{0-inf} \times BSA$ (pg*h*m^2/mL) Mean (SD)
B17MP							
Children (N = 25)	2160.7 (504.7)	2496.2 (621.9)	740.0 (224.3)	0.50 (0.25−1.00)	2.6 (0.7)	2426.1 (567.9)	2815.3 (759.9)
Adolescents (N = 28)	3373.2 (629.5)	3876.42 (685.24)	997.8 (246.8)	0.50 (0.25−2.00)	2.6 (0.6)	5222.5 (945.6)	6026.4 (1182.7)
Adults (N = 28)	2394.7 (555.0)	3019.0 (736.0)	590.5 (142.4)	0.75 (0.25−2.00)	3.5 (0.7)	4513.5 (886.9)	5697.4 (1245.7)
Formoterol							
Children (N = 26)	162.5 (45.4)	208.4 (59.3)	74.7 (20.2)	0.25 (0.25−0.28)	3.6 (0.7)	181.1 (37.7)	232.7 (53.6)
Adolescents (N = 28)	106.0. (28.4)	142.7 (41.2)	52.3 (18.3)	0.25 (0.25−1.05)	4.0 (0.9)	162.8 (37.6)	219.6 (58.0)
Adults (N = 30)	86.7 (18.0)	121.0 (24.7)	39.9 (9.0)	0.25 (0.25−0.27)	4.7 (1.7)	164.1 (33.6)	230.0 (50.4)

AUC = Area under the plasma drug concentration−time curve; C_{max} = maximum plasma concentration; t_{max} = time to maximum plasma concentration; $t_{1/2}$ = half-life; BSA = body surface area calculated according to the Mosteller formula.

correlates inversely with age and body size. Thus, increasing blood levels of the active components were observed with decreasing age and BSA. These findings suggest that anti-asthmatic dry powder dosage regimens should be adjusted for age and body size to avoid high systemic drug levels in children.

Interpretation

In this study the systemic exposure to the active ingredients of BDP/formoterol after DPI administration in children as compared to adults was almost doubled for formoterol and similar for B17MP despite the halved BDP dose administered in children. Although more modest, the systemic exposure

after BDP/formoterol DPI administration was also higher in adolescents as compared to adults. After normalization of the systemic exposure for BSA, the same nominal dose of formoterol administered with DPI in children, adolescents and adults led to equivalent exposures in the three populations, while a halved dose of BDP in children led to halved exposure of B17MP in comparison to adolescents and adults.

The PK properties of inhaled drugs assuming monocompartmental distribution in the body after absorption to the systemic circulation depends on the volume of distribution of the drug in the body (reasonably proportional to the BSA), the total amount of drug absorbed systemically, the total systemic exposure (AUC) and the elimination constant (λz) calculated as 0.693/half-life of the drug [13]:
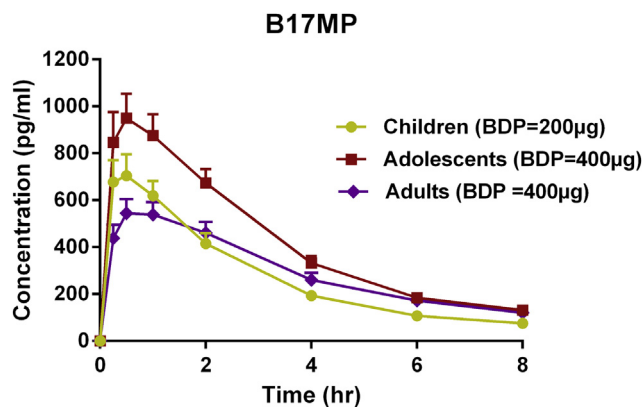

Figure 1 Beclometasone-17-monopropionate (B17MP) plasma profiles. Average plasma concentrations (95% confidence intervals) after four inhalations of beclometasone-dipropionate/formoterol DPI (50 μg/6 μg in children and 100 μg/6 μg in adolescents and adults) for a total single beclometasone-dipropionate dose of 200 μg in children and 400 μg in adolescents and adults.
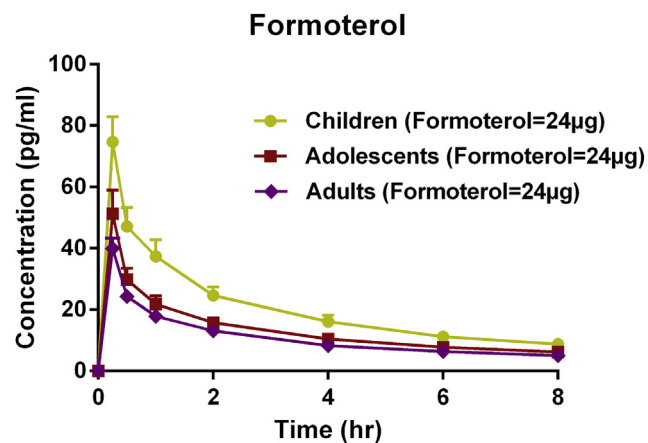

Figure 2 Formoterol plasma profiles. Average plasma concentrations (95% confidence intervals) after four inhalations of beclometasone-dipropionate/formoterol DPI (50 μg/6 μg in children and 100 μg/6 μg in adolescents and adults) for a total single formoterol dose of 24 μg in each age group population.

Table 3 Pharmacokinetic (PK) analysis of beclometasone 17-monopropionate (B17MP) and formoterol after administration of beclometasone-dipropionate/formoterol DPI in children and adolescents vs. adults.

Test	PK variable	B17MP		Formoterol	
		Point estimate	90% CI	Point estimate	90% CI
Adolescents/adults	AUC_{0-t}	1.42	1.28–1.57	1.20	1.08–1.35
	AUC_{0-inf}	1.30	1.18–1.44	1.15	1.03–1.30
	$AUC_{0-t} \times BSA$	1.16	1.06–1.27	0.99	0.90–1.09
	$AUC_{0-inf} \times BSA$	1.06	0.96–1.18	0.95	0.85–1.05
	C_{max}	1.68	1.50–1.89	1.27	1.11–1.44
Children/adults	AUC_{0-t}	0.90	0.81–1.00	1.85	1.64–2.07
	AUC_{0-inf}	0.83	0.74–0.92	1.69	1.50–1.90
	$AUC_{0-t} \times BSA$	0.53	0.48–0.59	1.10	1.00–1.22
	$AUC_{0-inf} \times BSA$	0.49	0.44–0.54	1.01	0.91–1.13
	C_{max}	1.23	1.09–1.39	1.86	1.62–2.13

The point estimate is calculated as ratio of the geometric means for the different PK parameters between the age group populations. AUC = Area under the plasma drug concentration–time curve; C_{max} = maximum plasma concentration; t_{max} = time to maximum plasma concentration; $t_{1/2}$ = half-life; BSA = body surface area calculated according to the Mosteller formula.

$$\text{Volume of distribution of the drug in the body compartment} = \text{Amount of drug absorbed into the body compartment}/(\text{AUC} \times \lambda z)$$

According to the PK equation, BSA × AUC is proportional to the amount of drug absorbed into the body compartment/λz. In the current study, BSA × AUC was equivalent in the three age group populations for both B17MP and formoterol and the half-lives were similar. It follows that the amount of drug absorbed to the bloodstream after administration of BDP/formoterol DPI is similar in the three age group populations with the net effect of a higher systemic exposure in younger patients with smaller BSA.

Contrasting the present findings previous similar investigations demonstrated that when using a pMDI with a spacer the amount of drug reaching the systemic circulation for the same nominal dose is lower in young patients resulting in similar systemic exposure in children,
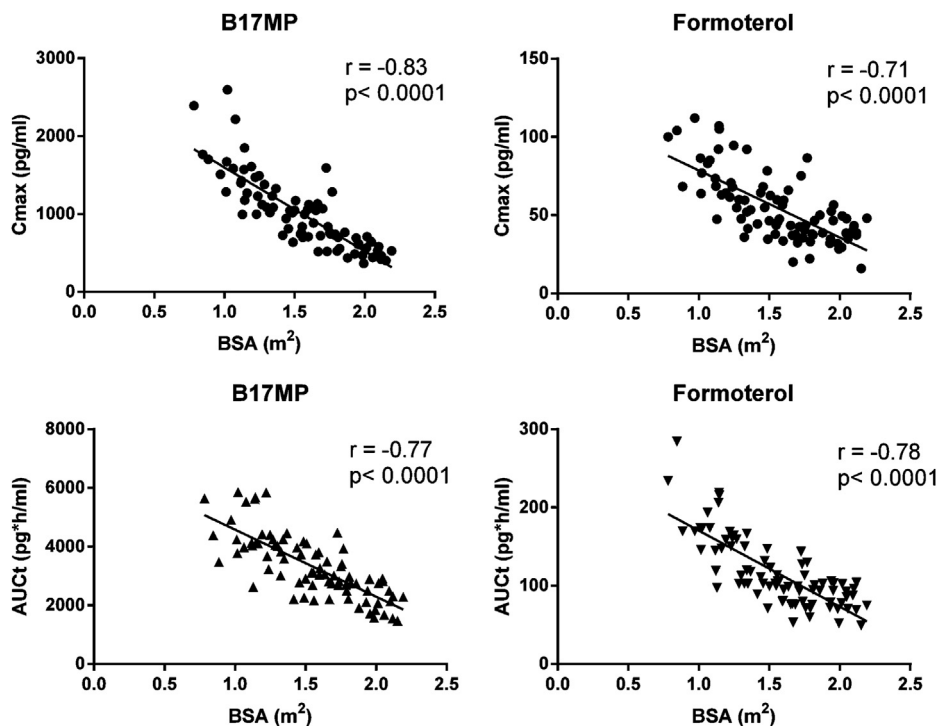

Figure 3 Correlation between exposure and body surface area. Correlation between the rate (C_{max}) and extent of exposure (AUC) to beclometasone-17-monopropionate (B17MP) and formoterol and the body surface area (BSA) of individual patients. Correlations were considered significant at $p < 0.05$ (Spearman's non-parametric test). In children the systemic exposure to B17MP was normalized to a beclometasone-dipropionate dose of 400 μg.

Figure 4 Correlation between exposure and age. Correlation between the rate (C_{max}) and extent of exposure (AUC) to beclometasone-17-monopropionate (B17MP) and formoterol and the body surface area (BSA) of individual patients. Correlations were considered significant at $p < 0.05$ (Spearman's non-parametric test). In children the systemic exposure to B17MP was normalized to a beclometasone-dipropionate dose of 400 μg.
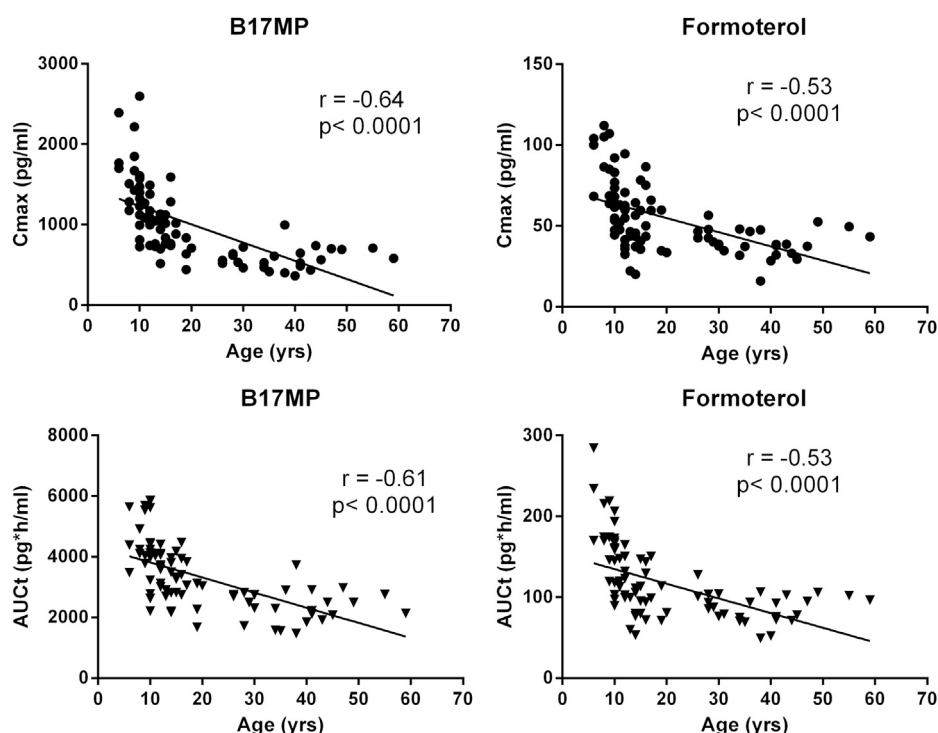
adolescents and adults [6,7]. Although it is well established that different inhaler devices may be used differently by patients, these diverging observations may be attributed to the different characteristics of the two ways of inhaling the drugs. Indeed, when inhaling an aerosol using a pMDI plus spacer the amount of drug reaching the lung is dependent on the inhalation time and tidal volume of the subject due to exponential emptying of the spacer [14]. As both inhalation time and tidal volume is lower in younger patients, this leads to comparable exposures among the different age groups. An additional explanation is that narrow upper airway geometry in children may have a filtering effect and subsequently lead to a decreased amount of aerosol penetrating into the lower airways compared to adults. This explanation is supported by an in vitro airway cast study showing that a decreased mass of fine particle aerosol passes through the cast of the upper airway of a child compared with the cast of the upper airway of an adult [15]. Differently, with the use of a breath actuated DPI [16], the age dependent respiratory capacity of the subject is less likely to influence the amount of drug reaching the lung resulting in systemic concentrations inversely correlated to the body size of patients. Regardless of the inhalation system, the upper airway dimensions of children may have a filtering effect on aerosol/dry powder penetration to the lungs.

For the paediatric pulmonologist treating childhood asthma these findings support guideline recommendations that ICS DPI dosage in the paediatric population should be adjusted to approximately half the adult dose to render similar systemic exposure. However, when prescribing ICS pMDI with a spacer to young children safety concerns should not prompt dose reduction as the systemic exposure in children is age and body size independent. Particular caution is warranted in the transition phase when the child with persistent asthma grows older and is shifted from pMDI plus spacer to a DPI to titrate the dose in order to achieve sufficient asthma control and preclude the occurrence of side effects [5,17,18].

Therefore it is important that dose recommendations specifically take into account the delivery device, i.e. advising dose adjustment when using DPI but not when using pMDI and spacer.

Strengths and limitations of the study

It is a limitation that this study assessed pharmacokinetics only and the correlation between systemic exposure and clinical safety profile is not fully established.

It is another limitation that data is pooled from two independent cross-over trials (one in children and one in adolescents and adults) designed to investigate PK bioequivalence between the fixed combination of BDP/formoterol DPI vs. the separate application of BDP and formoterol DPIs. Due to this and the limited amount of study subjects, replication of the findings is necessary.

It is an advantage that the studies were conducted under strictly standardized conditions according to the European Medicines Agency's "Guideline on the Investigation of

Bioequivalence" [12] and with external monitoring according to the ICH GCP guidelines. The storage, preparation and administration of the study drug were consistent in the two studies, which were performed by a small highly trained team handling all procedures according to pre-defined standard operating procedures. The blood samples were processed identically in the studies and all samples were analyzed in the same laboratory with the same methods. Also, the study drug was administered in the morning at approximately the same time in all the trials to minimize any circadian variation in PK parameters [19]. The minimum wash-out period of 7 days eliminated the risk of carry-over effect taking into account 5 times the terminal half-life [12].

Conclusion

The systemic exposure to the active ingredient of BDP (B17MP) and formoterol after dry powder inhalation in asthmatic children, adolescents and adults correlates inversely with age and body size resulting in increased blood levels in younger patients. This suggests that anti-asthmatic dry powder dosage regimens for children should be adjusted for age and body size to avoid high systemic drug levels and subsequent risk of unwanted side effects.

Source of funding

Chiesi Farmaceutici S.p.A. funded the study.

Contributions

BC, EKM, NV, PP, LM, EN, AD, MD, AB, NS, NS, DS, HB are responsible for data acquisition, analysis, interpretation and writing the manuscript. MG, AP, FS, GC, GP, DA were responsible for study design, data analysis, interpretation and writing of the manuscript. All co-authors have contributed substantially to the analyses and interpretation of the data, and have provided important intellectual input and approval of the final version of the manuscript.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: BC has received payment from Chiesi Farmaceutici S.p.A. in excess of 10 000 Euro for consulting; and travel to the ERS congress 2010 was funded by Chiesi Farmaceutici S.p.A. HB has received honorarium in excess of 10 000 Euro for consulting. DS has received sponsorship to attend international meetings, honoraria for lecturing or attending advisory boards and research grants from Chiesi Farmaceutici S.p.A. Beside the above mentioned, BC, HB and DS had no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work. MG, AP, FS, GC, GP, DA are all currently employed at Chiesi Farmaceutici S.p.A. EKM,

NHV, PP, LM, EN, AD, AB, MD, NLS and NS had no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.05.007.

References

[1] Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, Gibson P, Ohta K, O'Byrne P, Pedersen SE, Pizzichini E, Sullivan SD, Wenzel SE, Zar HJ. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 2008 Jan;31(1):143—78.

[2] Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de BJ, de Jongste JC, Eber E, Everard ML, Frey U, Gappa M, Garcia-Marcos L, Grigg J, Lenney W, Le SP, McKenzie S, Merkus PJ, Midulla F, Paton JY, Piacentini G, Pohunek P, Rossi GA, Seddon P, Silverman M, Sly PD, Stick S, Valiulis A, van Aalderen WM, Wildhaber JH, Wennergren G, Wilson N, Zivkovic Z, Bush A. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J 2008 Oct; 32(4):1096—110.

[3] Pedersen SE, Hurd SS, Lemanske Jr RF, Becker A, Zar HJ, Sly PD, Soto-Quiroz M, Wong G, Bateman ED. Global strategy for the diagnosis and management of asthma in children 5 years and younger. Pediatr Pulmonol 2011 Jan;46(1):1—17.

[4] Volovitz B, Amir J, Malik H, Kauschansky A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. N Engl J Med 1993 Dec; 329(23):1703—8.

[5] Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC. Effect of inhaled glucocorticoids in childhood on adult height. N Engl J Med 2012 Sep;367(10):904—12.

[6] Onhoj J, Thorsson L, Bisgaard H. Lung deposition of inhaled drugs increases with age. Am J Respir Crit Care Med 2000 Nov; 162(5):1819—22.

[7] Govoni M, Piccinno A, Lucci G, Poli G, Acerbi D, Singh D, Kuna P, Chawes B, Bisgaard H. The systemic exposure to inhaled beclometasone/formoterol pMDI with valved holding chamber is independent of age and body size. Pulm Pharmacol Ther 2014 Apr 16 [ahead of print].

[8] Global Initiative for Asthma (GINA), National Institute of Health, National Heart Lung and Blood Institute (NHLBI)/World Health Organisation (WHO). Global strategy for asthma management and prevention. Workshop report, updated 2011. Available on www.ginasthma.org. Downloaded 4th Oct 2013.

[9] Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3—95-yr age range: the global lung function 2012 equations. Eur Respir J 2012 Dec;40(6):1324—43.

[10] Chawes B, Piccinno A, Kreiner-Moller E, Vissing N, Poorisrisak P, Mortensen L, Nilson E, Bisgaard A, Dossing A, Deleuran M, Skytt N, Samandari N, Sergio F, Ciurlia G, Poli G, Acerbi D, Bisgaard H. Pharmacokinetic comparison of inhaled fixed combination vs. the free combination of beclometasone

and formoterol pMDIs in asthmatic children. Br J Clin Pharmacol 2013 Apr;75(4):1081—8.

[11] El ER, Lindemalm S, Eksborg S. Estimation of body surface area in various childhood ages — validation of the Mosteller formula. Acta Paediatr 2012 May;101(5):540—4.

[12] Guideline on the Investigation of Bioequivalence. Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/Corr ** — EMA — 2010. Downloaded 4th Oct 2013.

[13] Clinical pharmacokinetics and pharmacodynamics: concepts and applications. 4th ed. Lippincott Williams & Wilkins; 2010.

[14] Schultz A, Le Souef TJ, Venter A, Zhang G, Devadason SG, Le Souef PN. Aerosol inhalation from spacers and valved holding chambers requires few tidal breaths for children. Pediatrics 2010 Dec;126(6):e1493—8.

[15] Berg E. In vitro properties of pressurized metered dose inhalers with and without spacer devices. J Aerosol Med 1995 Sep;8(Suppl. 3):S3—10.

[16] Zuccaro F, Sergio F, Petruzzelli S, Singh D. Therapeutic equivalence of beclometasone dipropionate/formoterol administered via NEXT™ DPI with beclometasone dipropionate/formoterol administered via HFA pMDI in adult asthmatic patients. Eur Respir J 2010;36(Suppl. 54):P4540.

[17] Bisgaard H. Long-acting beta(2)-agonists in management of childhood asthma: a critical review of the literature. Pediatr Pulmonol 2000 Mar;29(3):221—34.

[18] Ni CM, Lasserson TJ, Greenstone I, Ducharme FM. Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database Syst Rev 2009; 3:CD007949.

[19] Kennaway DJ, Royles P. Circadian rhythms of 6-sulphatoxy melatonin, cortisol and electrolyte excretion at the summer and winter solstices in normal men and women. Acta Endocrinol Copenh 1986 Nov;113(3):450—6.