

Accepted Date : 08-Sep-2015
Article type : Review Article

Extra fine particle inhaled corticosteroids, pharmacokinetics and systemic activity in children with asthma

Ole D. Wolthers

Asthma and Allergy Clinic,
Children's Clinic Randers,
Randers, Denmark

Corresponding author:

Ole D. Wolthers

Honorary Assistant Professor, Consultant Paediatrician, MD, DMSci, BTh

Asthma and Allergy Clinic,

Children's Clinic Randers,

Dytmaersken 9,

DK-8900 Randers,

Denmark

Telephone: +45 87 10 08 08

E-mail: akk.odws@dadlnet.dk

Short title: Extra fine inhaled steroids

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12491

This article is protected by copyright. All rights reserved.

Ole D. Wolthers.

Extra fine particle inhaled corticosteroids, pharmacokinetics and systemic activity in children with asthma

Pediatr Allergy Immunol

Abstract

Background: During recent years extra fine particle inhaled corticosteroids with a median aerodynamic diameter $\leq 2 \mu\text{m}$ have been introduced in the treatment of asthma. The aim of this paper was to review pharmacokinetics and systemic activity of extra fine particle hydroalkane pressurised metered dose inhaled (pMDI) ciclesonide and beclomethasone dipropionate in children.

Methods: A literature review.

Results: Systemic bioavailability of oral and pulmonary deposition of extra fine ciclesonide and beclomethasone dipropionate was 52 and 82%, the half life in serum 3.2 and 1.5 hours and first pass hepatic metabolism $>99\%$ and 60% , respectively. Secondary analyses of urine cortisol/creatinine excretion found no effects of ciclesonide pMDI between 40 and 320 $\mu\text{g/day}$ or of beclomethasone dipropionate pMDI between 80 and 400 $\mu\text{g/day}$. Ciclesonide pMDI 40, 80 and 160 $\mu\text{g/day}$ caused no effects on short term lower leg growth rate as assessed by knemometry. Ciclesonide 320 $\mu\text{g/day}$ was associated with a numerically short term growth suppression equivalent to 30% which was similar to 25 and 36% suppression caused by beclomethasone dipropionate HFA and CFC 200 $\mu\text{g/day}$, respectively.

Conclusions: Consistent with the differences in key pharmacokinetic features beclomethasone dipropionate is associated with a systemic activity detected by knemometry at a lower dose than ciclesonide. Whether that correlates with a clinically important difference remains to be explored. Assessments of systemic activity of beclomethasone dipropionate $<200 \mu\text{g/day}$ and of ciclesonide $>180 \mu\text{g/day}$ as well as

Accepted Article

head-to-head comparisons are warranted. Preferably, such studies should apply the sensitive method of knemometry.

Key words: inhaled corticosteroids, pharmacokinetics, systemic activity, bioavailability,

fine particle, knemometry, cortisol, ciclesonide, beclomethasone dipropionate, asthma.

Name and address of the author to whom requests for offprints should be sent:

Ole D. Wolthers

Honorary Assistant Professor, Consultant Paediatrician, MD, DMSci, BTh

Asthma and Allergy Clinic,

Children's Clinic Randers,

Dytmaersken 9,

DK-8900 Randers,

Denmark

Telephone: +45 87 10 08 08

E-mail: akk.odws@dadlnet.dk

Introduction

Inhaled corticosteroid pressurised metered dose inhalers (pMDI) have been used in the treatment of children with asthma for more than three decades. The drugs have improved asthma management considerably (1). However, it has also become clear that inhaled corticosteroids have a potential for systemic activity as evidenced by

Accepted Article

measures of hypothalamic-pituitary-adrenal function (2,3) and short term growth (4,5). In the early 1990's the first randomised, double blind trials reporting dose related suppressive effects of inhaled corticosteroids on short term growth were published (4,5). It took more than two decades of further clinical research for the observation to become generally accepted by the scientific community (6) and present guidelines unanimously focus on dose aspects of inhaled corticosteroids to reduce adverse effects on longitudinal growth (7,8). The research leading to the current recommendations has mainly been on chloroflourocarbon propelled pMDIs and dry powder inhalers which have a greater particle size than hydroflouroalkane propelled pMDIs which were more recently introduced (9-11). Since pulmonary deposition of an inhaled drug is improved by fine particle modulations pharmacokinetics and systemic activity may be affected (2,3). The aim of this literature review was to review pharmacokinetics and systemic activity as assessed by measures of hypothalamic-pituitary-adrenal function and short term growth of extra fine particle inhaled corticosteroids in children with asthma.

Literature search

The following databases were used in the literature search: PubMed, a service of the National Library of Medicine, New York, USA, includes over 23 million citations for biomedical articles from the 1950s up to present times. The search was concluded on April 8 2015. The citations are from MEDLINE and additional life science journals and The Cochrane Library. The following search terms were used: inhaled glucocorticosteroids, inhaled steroids, inhaled corticoids, inhaled glucocorticoids, beclomethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, flunisolide, triamcinolone acetonide, ciclesonide, extra fine particles, asthma,

Accepted Article

paediatric asthma, median mass aerodynamic parameter, fine particle fraction, hypothalamic-pituitary function, cortisol, growth, short term growth, knemometry, systemic activity, bioavailability. The literature was also studied by manual searches of reference lists for reviews and meta-analyses. Selected references contained primary original, randomised, doubled-blind data or were based on open, randomised studies, reviews, chapters in text books, meta-analyses, Cochrane publications, guidelines and consensus reports. Studies on particle size were selected with the aim of introducing the concept to clinicians and others who may have no research experience in the area themselves. In addition to pharmacokinetic studies in children studies in adults and experimental in vitro studies were selected as pharmacokinetic studies in prepubertal children (<12 years of age) were few. Since there was a paucity of some aspects of pharmacokinetic data on inhaled corticosteroids review papers which have added information in areas where specific data have not been published were selected. All available studies of hypothalamic-pituitary-adrenal function and short term growth in prepubertal children (<12 years of age) treated with extrafine inhaled corticosteroids were selected, none were excluded; and all available results based on primary or secondary measures in the studies were included.

Particle size

Emitted particles from an inhaler device are not of a uniform size. They may vary from <1 to >10 μm (12-14). To be in the respirable range, i.e. to be deposited throughout the airways, the particles should be smaller than 5 μm , larger particles are prone to being deposited in the mouth and throat (12-14). Extra fine particles have been suggested to penetrate better into small, peripheral airways with a diameter

below 2 μm explaining findings of a more homogeneously distributed intra-pulmonary deposition in healthy adults (14) and in children with asthma ≥ 5 years of age (15). In accord with this, fine particle size drugs are defined as having a median mass aerodynamic diameter (MMAD) of $\leq 5 \mu\text{m}$, extra fine particle modulations as having a diameter $\leq 2 \mu\text{m}$ (11).

Measure of particle size

The measures median mass aerodynamic diameter (MMAD) and fine particle fraction (FPF) are used to describe the distribution of particle sizes in emissions from inhaler devices (16). The measures are based on in vitro assessments of particle distribution by the 8-stage Andersen Cascade Impactor (16,17). MMAD is defined as the median diameter of a dose delivered to the 8-stage Andersen Cascade Impactor exclusive of the throat of the impactor; FPF is the percentage of delivered dose inclusive of the throat with a particle diameter $<5 \mu\text{m}$ (17). Though such in vitro derived descriptions may be said to be supported by in vivo suggestions of increased intrapulmonary deposition rates in adults and schoolchildren (14,15) as well as in an infant lung model (18) attempts to correlate measures such as MMAD $<5 \mu\text{m}$ with in vivo measures of lung deposition have been difficult to achieve. There is no agreement as to which measure is the more sensitive in relation to predicting in vivo distribution of an inhaled drug in the lungs and only surrogate markers such as particle imaging-based techniques are available for the prediction (19). A preliminary report suggested that FPF may correlate better with peripheral lung deposition than MMAD, however, that needs further research (20).

MMADs of currently available inhaled corticosteroids are presented in table 1 (14,16,21-26). The data on Giona Easyhaler® and Relvar Ellipta® have not been

published, however, they were given in e-mails from Susanne Ladefoged Christensen, Jacobsen Pharma & MedTech Advice A/S, Denmark, March 4 2015, and Medical Information, GlaxoSmithKline Pharma A/S, Denmark, May 18 2015. Data on mometasone furoate have not been published, and it was not possible to provide any data otherwise. Hydroflouroalkane flunisolide was indicated to have a MMAD of 1.2 μm , however, it was taken off the market in the US in 2011 and is not available in Europe.

Variations in particle size measures

When MMAD data are evaluated it is important to consider that MMAD is not a static measure. It is decreased by high inhalation flow rates (16), increased by a high relative humidity, whereas increasing temperature from 20°C to 40°C in an in vitro model resulted in indications of reductions in MMAD and increased pulmonary deposition of solution pMDIs with generally no effect on deposition of a suspension pMDI (27). This has the important implication that dependent on such factors MMAD may vary around 50% (16) challenging the <2 μm cut-off definition of extra fine modulations. This suggests that the cut off level of measures defining fine and extra fine inhaled corticosteroids is fluctuating and that the definition of extra fine corticosteroids cannot be defined by a specific diameter. That needs to be considered when interpreting the data in table 1.

Though most of the MMADs of the listed inhaled drugs have not been compared head-to-head, and though methodological inconsistency may affect the data it is generally understood that the hydroflouroalkane pMDI suspensions of ciclesonide (CIC) and beclomethasone dipropionate (BDP) are the only extra fine particle modulations available at present (2, 28,29).

Pharmacokinetics

A flowchart of the literature search is given in the figure. The data were derived from in vitro studies (33,34,37); from studies in healthy males (30-32) and healthy males and females (40); from studies in males and females (40) and children (36,38) with asthma; and from review papers (2, 35, 39). The studies in adults comprised populations of 6 (30), 8 (31), 9 (32) and 12 (40) subjects; the pediatric studies 18 (36) and 34 (38) prepubertal children. Treatments were single doses of 6.9 mg (oral administration) and 0.64 mg (intravenous administration) ciclesonide (30); a single dose of ciclesonide 40 µg (31); 6 days treatment with 50 and 100 µg beclomethasone dipropionate (32); a single dose of 1280 µg ciclesonide (40); a single dose of 200 and 400 µg beclomethasone dipropionate (36); and 7 days treatment with ciclesonide 80 and 160 µg/day (38). Pharmacokinetic key data of extra fine ciclesonide and beclomethasone dipropionate are given in table 2 (2, 30-40).

Both ciclesonide and beclomethasone dipropionate are prodrugs which are activated by esterase enzymes in the intrapulmonary epithelium to the active forms des-isobutylol-ciclesonide (des-CIC) and beclomethasone-17-monopropionate (17-BMP), respectively (2,30). The metabolite beclomethasone-21-monopropionate (21-BMP) has little and beclomethasone (BOH) no pharmacological activity, and pharmacokinetic data have mostly been based on assessment of 17-BMP.

Bioavailability

When a metered dose inhaler is activated or a dose is inhaled from a dry powder device

part of the dose is retained in the inhaler and does not reach the patient. *The delivered*

dose is the amount of drug that reaches the patient. When a drug is inhaled the amount of

drug that reaches the lungs is lower than the delivered dose. The rate of *pulmonary*

deposition varies from <10% in chloroflourocarbon to more than 50% of the delivered dose

in extra fine hydroalkane driven pMDIs (2,30-32). Virtually all drug deposited in the lungs is absorbed to the systemic circulation constituting a *bioavailability of pulmonary deposition* of 100%. Compared to beclomethasone dipropionate a lower percentage of

ciclesonide is converted to the active metabolite prior to absorption to the systemic

circulation resulting in detectable plasma concentrations of both CIC and des-CIC,

whereas virtually no beclomethasone dipropionate becomes systemically detectable (2). A

part of the delivered dose is deposited in the oropharyngeal cavity where it is swallowed

and absorbed from the gut. The amount of drug that escapes *first pass hepatic metabolism*

becomes systemically available and is designated *bioavailability of oral deposition*. Due to

differences in first pass hepatic metabolism rates bioavailability of oral deposition varies

between specific corticosteroids, the highest rates being found in beclomethasone

dipropionate regardless of the formulation (2). Most corticosteroids as ciclesonide undergo

extensive first pass metabolism to inactive metabolites. However, a great part of

swallowed BDP is metabolized to the active form 17-BDP which explains why *systemic*

bioavailability of oral and pulmonary deposition rates of 82% for extra fine beclomethasone

dipropionate have been found as compared to 52% for ciclesonide (2).

Pulmonary retention

Intracellular reversible fatty acid *esterification* of inhaled corticosteroids has been suggested as a mechanism by which corticosteroids can be retained longer in the lungs,

thus increasing *pulmonary retention time* and the duration of action (33). The formation of

esters, i.e. lipid conjugation, depends on the presence of a hydroxyl group at position 21 of

the corticosteroid molecule which is a feature of des-CIC and 17-BDP. In accord with that

esterification has been reported in both active metabolites (34,2). The hypothesis of a

possible association between esterification and duration of pharmacological activity,

however, has not been definitely proven. On the contrary, it has been suggested that

esterification may not be important because, potentially, it may reduce the concentration of

the active drug (2).

Inhaled corticosteroids penetrate the phospholipid bilayer of cell membranes in the intrapulmonary epithelium to bind with the intracellular glucocorticoid receptor. The rate of

uptake depends on a number of factors such as molecular size, charge and configuration

and *lipophilicity* of the molecule (35). *Receptor binding affinity*, pulmonary retention time

and duration of action, thus, depend on lipophilicity. Lipophilicity can be difficult to measure

and comparisons of lipophilicity data in corticosteroids need to be interpreted with

caution (33). It remains to be clarified whether the observed data on des-CIC and 17-BDP

correlate with significant differences in duration of action and pharmacological activity (2).

The higher the degree of lipophilicity of a corticosteroid, however, the longer also the retention time in other tissues in the body which may contribute to an accumulation of

active drug which may be associated with an increase in systemic activity (36). In a rat

model des-CIC was still detected 24 hours after dosing (37). The retention time for 17-BDP

is considered to be some hours (2), however, specific data are not available.

Protein binding

The plasma protein binding of inhaled corticosteroids is being considered important

since it is the unbound fraction only that is expected to have pharmacological activity. The

plasma protein binding of des-CIC of 99% and 17-BDP of 96% is regarded as being in the

high and medium range, respectively. Therefore, it has been speculated that the high

binding rate of des-CIC would reduce the systemic activity of the molecule (39).

There are,

however, no data to support the hypothesis or to suggest that the difference has any

implications for systemic activity of the drugs.

Clearance

Plasma clearance is a measure of elimination of a drug from the body. The maximum

clearance of a corticosteroid via hepatic clearance alone is approximately 90 L/h which is

close to the rate of hepatic flow itself (39,40). The reported clearance rates of des-CIC and

17-BDP (table 2) are high, thus suggesting extra-hepatic metabolism (39, 40).
Studies

assessing once daily administration of extra fine ciclesonide (36) and

Accepted Article

beclomethasone dipropionate (38) in doses of 160 µg and 200 µg, respectively, in 5-11 (36) and 9-12 years old children with asthma (38) found the active metabolites to be detectable in serum up to 12 (36) and 6 hours (38) later. Though the bioavailability of the two molecules are high the systemic exposure may be less than would be expected due to their clearance as compared to other corticosteroids (2). Theoretically, the higher clearance rate the higher the therapeutic index, however, there are no data to suggest that differences in plasma clearance rates per se may discriminate between inhaled corticosteroids with respect to systemic activity.

Half-life

Half-life of a drug is defined by the time it takes for the concentration of the drug to decline by one half of its previous value. The half-life of an inhaled corticosteroid is a function of plasma clearance and the volume of distribution of the drug (39), thus, it is a secondary measure depending on other pharmacokinetic factors. An increase in half-life results in increased pulmonary retention time and duration of action. However, it also increases the time that the drug is detectable in the systemic circulation and results in a longer duration of action at the glucocorticoid receptor in other tissues than lungs (2). There are no data to link differences in half-life of inhaled corticosteroids to variations in systemic activity of the drugs.

Systemic activity

Systemic activity of inhaled corticosteroids in children with asthma have mostly been investigated by non-invasive measures of hypothalamic-pituitary-adrenal function

and short term lower leg growth, knemometry (41,42). A flowchart of the literature search

is given in the figure. None of the assessments of hypothalamic-pituitary-adrenal function,

however, were primary measures. Four knemometry studies were identified in which

lower leg growth rate was the primary outcome measure. A summary of the knemometry

studies is given in table 3.

Hypothalamic-pituitary-adrenal function

Systemic activity of extra fine ciclesonide between 40 and 320 µg/day (10, 43-47)

and beclomethasone dipropionate between 80 and 400 µg/day (9,48-50) have been assessed by single morning plasma concentrations and Synacthen stimulation of the

hypothalamic-pituitary-adrenal axis (43,44,47) and by 12- (44) or 24- (10,47,50) hour

urine cortisol excretion in randomized, double blind (10,43-48,50) and randomized,

open designs (49-51) in prepubertal school age children with asthma. In all studies of

ciclesonide except one (45) the pMDI was used without a volume spacer once

daily in the evening; the studies in beclomethasone dipropionate used a volume spacer

and the pMDI was taken twice daily. Most of the studies did not find any

effects on cortisol measures be it when compared to placebo (43-48) or treatment free

run in (50) or when compared to conventional beclomethasone dipropionate in twice the

daily dose (49) or to fluticasone propionate (45). One study in 6-11 year old children,

however, found ciclesonide 80 µg/day and 160 µg/day to suppress 24-h urine cortisol

statistically significantly as compared to fluticasone propionate 176 µg/day (10) and

another study compared ciclesonide 160 µg/ to dry powder budesonide 400 µg/day with

similar results (46). Randomized studies of ciclesonide in children 2-6 years of age and of

beclomethasone dipropionate in children 5-12 years of age did not state how urine cortisol

was sampled or measured and did not give any data to support their observations of no

effects of the treatments (9,51).

Knemometry

In children the 12- and 24-hours urine free cortisol excretion measures are less

sensitive than short term knemometry as proven by rigorous comparisons (52,53) and as

confirmed by numerous randomized short term knemometry trials (42). The

knemometer measures the length of the lower leg (42). When validated recommendations

for standardisation and measurement procedures are used knemometry is a highly

accurate and reproducible method for assessment of systemic activity of inhaled

corticosteroids (42). All available published knemometry data on extra fine modulations

have been derived from crossover study designs using 2 weeks treatment periods.

Ciclesonide

A randomized double blind 2-week periods cross over knemometry study of extrafine

ciclesonide in doses of 40, 80 and 160 µg from a pMDI without a volume spacer taken

once daily in the evening by 24 6-12 year old children with mild asthma found no

statistically significant effects of any of the doses when compared to placebo (44). Mean

growth rates during all active periods were virtually identical with placebo growth. In a

similar placebo controlled design with similar number and ages of the study subjects

ciclesonide 160 µg pMDI with a volume spacer twice daily was compared to fluticasone

propionate pMDI with an identical volume spacer dosed as 220 µg in the morning and 125

µg in the evening (45). Mean lower leg growth rates were suppressed by 30 and 82%

during ciclesonide and fluticasone propionate, respectively, however only the fluticasone

propionate treatment reached statistical significance. The studies were not designed in

accord with recommendations for equivalence studies and as admitted by the authors

themselves a power calculation was not carried out for study planning (45).

Beclomethasone dipropionate

An observer blinded, randomized cross over comparison of extra fine hydroflouroalkane

beclometasone dipropionate 100 µg b.i.d. pMDI with the AeroChamber Plus[™] spacer with

chloroflourocarbon beclomethasone dipropionate 200 µg b.i.d with the Volumatic[™] spacer

used a non-inferiority design in 63 children 5-11 years of age with mild asthma (50). Extra

fine beclometasone dipropionate 100 µg b.i.d. was found to be non-inferior to

conventional beclomethasone dipropionate 200 µg b.i.d, and as compared to the treatment

free run in mean lower leg growth was suppressed by 25 and 36%, respectively, both

being at a statistically significant level (secondary analyses). The findings could not have

been confounded by the use of different spacers since a previous study found knemometry

rates to be non-inferior between hydroflouroalkane beclomethasone dipropionate $\mu\text{g/day}$

from the AeroChamber Plus[™] and from the Volumatic[™] spacer (54). The short term growth

suppressive effect of extra fine hydroflouroalkane beclomethasone dipropionate has been

further corroborated by a recent non-inferiority study with a similar design in 48 5-11 year

old children who received 100 μg b.i.d delivered from the Autohaler® which caused growth

to be suppressed by 37% as compared to a treatment free run in (55).

Two further knemometry studies were performed with a hydroflouroalkane beclomethasone dipronionate pMDI modulation that was originally thought to have a median mass aerodynamic diameter in the range of 3-4 μm which would support 1:1

systemic activity ratio with the chlorofluorocarbon driven formulations (56-59). A randomized

double blind non-inferiority trial in 7-12 year old prepubertal children with mild asthma

found lower leg growth rate to be non-inferior between hydroflouroalkane and chlorofluorocarbon beclomethasone dipropionate 200 $\mu\text{g/day}$ with the Volumatic[™] spacer

(56). As compared to run in growth rate suppression was 36 and 31%, respectively. The

growth suppression was considerably more marked when the same doses were taken

without a spacer by a similar study population in an identical design, the suppression being 79 and 77% by the hydroflouroalkane and chlorofluorocarbon formulations. The

suppression observed when a volume spacer was not used was as marked as the

Accepted Article
suppression caused by a dry powder formulation of beclomethason dipropionate (57,60).

The differences were explained by a volume spacer dependent reduction in oral deposition

rate and, thus, a lower bioavailability of oral deposition (2). Furthermore, in both studies

secondary analyses also found a statistically significant suppression of chlorofluorocarbon beclomethasone dipropionate 400 µg/day as compared to run in, whereas statistically

significant differences between chlorofluorocarbon doses of 200 and 400 µg were not

detected (54,57).

Discussion

Experimental data on pharmacokinetic features such as esterification, lipophilicity, receptor binding and half-life at the glucocorticoid receptor may be as relevant to paediatric as to adult populations. Pharmacokinetic data on extrafine ciclesonide and beclomethasone dipropionate, however, should be evaluated with caution as few of them have been derived from studies in children (36,38). Pulmonary deposition rates, bioavailability of oral and pulmonary deposition and the extent of first pass hepatic metabolism may vary between children and adults (2,61,62), and direct dose-to-dose comparisons of ciclesonide and beclomethasone dipropionate are not available.

During the ciclesonide research and development program focus was on potential pharmacokinetic features which have been suggested to differentiate ciclesonide from

other inhaled corticosteroids (18,63). Especially, features like a long retention time in the

lungs, esterification, high plasma protein binding and fast clearance have been taken to

support once daily dosing which in combination with an expected improvement in

adherence rate due to a once daily dosing regimen have been taken to suggest a

reduced systemic activity of ciclesonide. There are, however, no data to support such

speculations (28,64). It appears that more than any factor, what decides the severity of

systemic activity of inhaled corticosteroids is the concentration of drug at the

glucocorticosteroid receptor in other tissues than the lungs (2).

Since hydrofluoroalkane inhaled corticosteroids deliver a great fraction of the drug to

the lungs and virtually all drug deposited in the lungs is absorbed to the circulation it

may not be surprising that sensitive knemometry studies have found suppression of short

term growth during treatment with 200 µg extra fine beclomethasone propionate to be non-

inferior to 200 µg from a conventional chlorofluorocarbon pMDI (50). Furthermore, when

the differences in bioavailability of oral and pulmonary desposition rates between

beclomethasone dipropionate and ciclesonide are considered as suggested from the

available data short term growth suppression should be expected at lower doses of

beclomethasone dipropionate than of ciclesonide. The pharmacokinetic profile of extra fine

beclomethasone dipropionate is associated with a higher systemic activity at a lower dose

than that of ciclesonide. Having said that, the observation of a lower leg growth rate

suppression of 30% in children treated with ciclesonide 320 µg/day does suggest a

detectable systemic activity of the drug. The finding needs to be challenged in a sufficiently

powered non-inferiority study design.

Though it may be argued that Synachten testing of the HPA axis may be a more clinically relevant measure of cortisol secretion it is considered obsolete for assessment of systemic activity of inhaled corticosteroids as is single plasma cortisol measurement. Serial blood assessments of cortisol, though invasive, and extended time period measures of cortisol excretion corrected for creatinine are more sensitive in detecting systemic activity (41,51). None of the published studies on urine cortisol/creatinine excretion in extra fine ciclesonide and beclomethasone dipropionate, however were designed or statistically powered to rigorously assess cortisol excretion. Future studies should be power calculated at detecting effects on cortisol excretion, and direct comparisons of extra fine ciclesonide and beclomethasone dipropionate are needed.

Considering that extra fine hydroalkane beclomethasone dipropionate and ciclesonide

pMDIs deposit a significantly higher proportion of the delivered dose to the intrapulmonary

airways than other inhaled corticosteroids and devices at their introduction it was hypothesized that asthma control might be achieved at a lower daily dose (49,65). Two

randomised controlled studies compared beclomethasone dipropionate with fluticasone

propionate pMDI in the same (9) or in the double dose (65) in children ≥ 5 years of age,

however, no statistically or clinically significant differences in the number of symptom free

days or exacerbations could be detected. One double blind trial in 6-11 year old children

found ciclesonide 80 µg/day and 160 µg/day to be non-inferior to fluticasone propionate

176 µg/day pMDI in FEV1 control and a number of secondary efficacy measures also did

not vary among the treatments (10). A double blind study in the same age group compared

ciclesonide 160 µg/day to dry powder budesonide 400 µg/day finding similar results (46).

Two studies compared ciclesonide 160 with fluticasone propionate 176 µg/day pMDI (66)

and ciclesonide 320 µg/day with budesonide pMDI 800 µg in adolescents up to 15 (66)

and 17 (67) years of age finding no differences in FEV1 or secondary efficacy markers.

The studies were in children with mild to moderate persistent asthma except one (67)

which was in individuals with severe asthma and which used doses which were probably

at the top flat part of the dose-response curve. So, extra fine ciclesonide or

beclomethasone dipropionate have not been proven more efficacious than

chlorofluorocarbon modulations or other inhaled drugs such as fluticasone propionate or

budesonide in children (28,64). In accord with that it appears that systemic activity profiles

have not been improved by the extra fine modulations of beclomethasone dipropionate.

Clinically important equivalents of urine cortisol and short term lower leg growth suppression would be suppression of the hypothalamic-pituitary-adrenal axis and long

term height growth. Clinical implications of inhaled corticosteroid induced urine cortisol

suppression, if any, have not been settled. An analysis based on randomised,

double blind short term knemometry and 1-year height growth studies indicated that inhaled corticosteroid suppression of short term lower leg growth rate of 25% or more implies a clinically relevant risk of long term height growth suppression of 1-2 cm during the first year of continuous twice daily treatment (42). The observations were supported by the only available randomised, double blind, placebo controlled study of final adult height after 4-6 years of continuous treatment with dry powder budesonide 400 µg/day which found a reduction in mean final height of 1.2 cm (68). Though the finding caused some worry, and though current guidelines may be said to reflect that (7,8), it seems fair to say that it has not yet been proven whether a height deficit of that size in fact is clinically important. Data to answer the question are needed. Having said that, short term knemometry assessments of extra fine ciclesonide and, especially, of beclomethasone dipropionate have highlighted the need for sufficiently powered and randomized long term height growth evaluations of extra fine particle inhaled corticosteroids in doses ≤ 400 µg/day.

In conclusion, consistent with the differences in key pharmacokinetic features beclomethasone dipropionate is associated with a systemic activity detected by knemometry at a lower dose than ciclesonide. Whether that correlates with a clinically important difference remains to be explored. Assessments of systemic activity of beclomethasone dipropionate <200 µg/day and of ciclesonide >180 µg/day as well as head-to-head comparisons are warranted. Preferably, such studies should apply the sensitive method of knemometry.

References

- 1) Carlsen KH. Pharmaceutical treatment of asthma in children. *Curr Drug Targets Inflamm Allergy* 2005; 4:543-9.
- 2) Daley-Yates PT. Pharmacological aspects of glucocorticoid therapy. In: Wolthers OD, editor. *Exogenous Glucocorticoids in Paediatric Asthma*. Kerala: Transworld Research Network, 2007, 1-18.
- 3) Wolthers OD, Daley-Yates PT. Hypothalamic-pituitary-adrenal axis function. In: Wolthers OD, editor. *Exogenous Glucocorticoids in Paediatric Asthma*. Kerala: Transworld Research Network, 2007, 19-33.
- 4) Wolthers OD, Pedersen S. Growth of asthmatic children during treatment with budesonide: a double blind trial. *Br Med J* 1991;303:63-65.
- 5) Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992;89:839-42.
- 6) Zhang L, Pruteanu AI, Prietsch SOM, Chauhan BF, Ducharme FM. Cochrane in context: Inhaled corticosteroids in children with persistent asthma: Effects on growth and dose-response effects on growth. *Evidence-Based Child Health* 2014;(4):1047-1051.
- 7) Global strategy for asthma management and prevention (revised May 2014): Global Initiative for Asthma (GINA). Available at: www.ginasthma.com. Accessed March 2015.
- 8) British guidelines on the management of asthma (revised October 2014). Available at: www.brit-thoracic.org.uk. Accessed March 2015.
- 9) van Alderen WM, Price D, De Baets FM, Price J. Beclomethasone dipropionate extra-fine aerosol versus fluticasone propionate in children with asthma. *Respir Med* 2007;101(7):1585-1593.
- 10) Pedersen S, Engelstätter R, Weber HJ, et al. Efficacy and safety of ciclesonide once daily and fluticasone propionate twice daily in children with asthma. *Pulm Pharmacol Ther* 2009;22(3):214-220.
- 11) Leach C, Colice GL, Luskin A. Particle size of inhaled corticosteroids: does it matter? *J Allergy Clin Immunol* 2009;124(suppl 6):S88-S93.
- 12) Newman SP, Chan HK. In vitro/in vivo comparisons in pulmonary drug delivery. *J Aerosol Med Pulm Drug Deliv* 2008;21:77-84.
- 13) Heyder J, Gebhart J, Rudolf G, Schiller CF, Stahlhofen W. Deposition of particles in the human respiratory tract in the size range 0.005-15 μm . *J Aerosol Sci* 1986;17:811-25.

- 14) Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12:1346-1353.
- 15) Devadason SG, Huang T, Walker S, Troedson R, Le Souëf PN. Distribution of technetium-99m-labelled QVAR delivered using an autohaler device in children. *Eur Respir J* 2003;21(69):1007-1011.
- 16) Johal B, Howald M, Fischer M, Marshall J, Venthoye G. Fine particle profile of fluticasone propionate/formoterol fumarate versus other combination products; the DIFFUSE study. *Comb Prod Ther* 2013;DOI 10.1007/s13556-013-0003-9.
- 17) European Pharmacopeia. Section 2.19. 18-Preparations for inhalation: Aerodynamic assessment of fine particles. *European pharmacopeia*. 3rd ed Suppl 2001. Strasbourg, France: Council of Europe;2002:113-24.
- 18) Janssens HM, De Jongste JC, Hop WC, Tiddens HA. Extra-fine particles improve lung delivery of inhaled steroids in infants: a study in an upper airway model. *Chest*. 2003 Jun;123(6):2083-2088.
- 19) Mitchell JP, Nagel MW. Improved laboratory test methods for orally inhaled products. *Ther Deliv* 2013;4(8):1003-1006.
- 20) Holsbeke CV, Marshall J, De Backer J, Vos W. Mass median aerodynamic diameter (MMAD) and fine particle fraction. Abstract published at the European Respiratory Society (ERS), Munich, Germany, September 6-10 2014.
- 21) Martin RJ. Therapeutic significance of distal airway inflammation in asthma. *J Allergy Clin Immunol* 2002;109:S447-S460.
- 22) Berger R, Berger WE. Particle size and small airway effects of mometasone furoate delivered by dry powder inhaler. *Allergy Asthma Proc* 2013;34(1):52-58.
- 23) Tamura G, Sakae H, Fujino S. In vitro evaluation of dry powder inhaler devices of corticosteroid preparations. *Allergol Int* 2012;61(1):149-154.
- 24) Cripps A, Riebe M, Schulze M, Woodhouse R. Pharmaceutical transition to non-CFC pressurized metered dose inhalers. *Respir Med* 2000;97(supplB):S3-S9.
- 25) Leach CL, Kuehl PJ, Chand R, Ketali L, Norenberg JP, McDonald JD. Characterization of respiratory deposition of fluticasone-salmeterol hydrofluoroalkane-134a and hydrofluoroalkane-134a beclomethasone in asthmatic patients. *Ann Allergy Asthma Immunol* 2012;108(3):195-200.
- 26) Drollmann A, Nave R, Stinijans VW, Baumgärtner E, Bethke TC. Equivalent pharmacokinetics of the active metabolite of ciclesonide with and without

- use of the Aerochamber Plus spacer in children. *Clin Pharmacokinet* 2006;45(7):729-736.
- 27) Shemirani FM, Hoe S, Lewis D, Church T, Vehring R, Finlay WH. In vitro investigation of the effect of ambient humidity on regional delivered dose with solution and suspensions MDIs. *J Aerosol Med Pulm Drug Deliv* 2013;26(4):215-222.
- 28) Boluyt N, Rottier BL, de Jongste JC, Riemsma R, Vrijlandt E, Brand PLP. Assessment of controversial pediatric asthma management options using GRADE. *Pediatrics* 2012;130(3):e658-e668.
- 29) Ivancsó I, Böcskei R, Müller V, Tamási L. Extrafine inhaled corticosteroid therapy in the control of asthma. *J Asthma and Allergy* 2013;6:69-80.
- 30) Nave R, Bethke TD, van Marle SP, Zech K. Pharmacokinetics of [¹⁴C]ciclesonide after oral and intravenous administration to healthy subjects. *Clin Pharmacokinet* 2004;43(7):479-486.
- 31) Leach CL, Bethke TD, Boudreau RJ, et al. Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. *J Aerosol Med* 2006;19(2):117-126.
- 32) Leach CL, Davidsson P, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. *Chest* 2002;122(2):510-516.
- 33) Miller-Larsson A, Jansson P, Runström A, Brattsand R. Prolonged airway activity and improved selectivity of budesonide possibly due to esterification. *Am J Respir Crit Care Med* 2000;162:1455-1461.
- 34) Nave R, Meyer W, Fuhst R, Zech K. Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. *Pulm Pharmacol Ther* 2005;18(6):390-396.
- 35) Edsbäcker S. Uptake, retention and biotransformation of corticosteroids in the lung and airways. In: Schleimer RP, O'Byrne PM, Szefer SJ, Brattsand R, eds. *Inhaled steroids in asthma. Optimizing effects in the airways*. New York:Marcel Dekker, Inc,2002:213-244.
- 36) Harrison LI, Kurup S, Chen LZ, Ekholm BP, Wighton TG, Shapiro GG. Pharmacokinetic comparison of beclomethasone dipropionate extrafine aerosol from two inhaler devices in children with asthma. *Eur J Clin Pharmacol* 2002;58(3):191-195.
- 37) Nave R, Meyer W, Fuhst R, Zech K. Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. *Pulm Pharmacol Ther* 2005;18(6):390-396.

- 38) Boss H, Minic P, Nave R., Similar results in children with asthma for steady state pharmacokinetic parameters of ciclesonide inhaled with or without spacer. *Clin Med Insights Pediatr* 2010;4:1-10.
- 39) Derendorf H, Hochhaus G, Meibohm B, Möllmann H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998;101 4 Pt 2):S440-446.
- 40) Nave R, Gunawardena KA, Zeth K, Bethke TD. Pharmacokinetic disposition of inhaled ciclesonide and its metabolite desisobutyryl-ciclesonide in healthy subjects and patients with asthma are similar. *Int J Clin Pharmacol Ther* 2006;44(1).1-7.
- 41) Wolthers OD, Honour JW. Hypothalamic-pituitary-adrenal function in children with asthma and rhinitis treated with topical glucocorticosteroids. *Clin Exper Allergy* 1998; 28: 545-550.
- 42) Wolthers OD. Methodology and implications of knemometry in growth assessment of inhaled glucocorticoids. *Pediatr Allergy Immunol* 2010 Feb;21(1 Pt 2):e190-8.
- 43) Pedersen S, Potter P, Dachev S, et al. Efficacy and safety of three ciclesonide doses vs placebo in children with asthma: The rainbow study. *Respir Medicine* 2010; 104:1618-1628.
- 44) Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. *J Allergy Clin Immunol* 2005;115(5):940-945.
- 45) Agertoft L, Pedersen S. Lower-leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate. *Pediatr Allergy Immunol* 2010;21:e199-e205.
- 46) von Berg A, Engelstätter R, Minic P, et al. Comparison of the efficacy and safety of ciclesonide 160 microg once daily in children with asthma. *Pediatr Allergy Immunol* 2007;18(5):391-400.
- 47) Gelfand EW, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr* 2006;148(3):377-383.
- 48) Nayak A, Lanier R, Weinstein S, Stampone P, Welch M. Efficacy and safety of beclomethasone dipropionate extrafine aerosol in childhood asthma: a 12-week, randomized, double-blind, placebo-controlled study. *Chest* 2002;122:1956-1965.
- 49) Pedersen S, Warner J, Wahn U, et al. Growth, systemic safety, and efficacy during 1 year of asthma treatment with different beclomethasone dipropionate formulations: an open-label, randomized comparison of

extrafine and conventional aerosols in children. *Pediatrics* 2002;109:e9.DOI:10.1542/peds.109.6.e92.

- 50) Wolthers OD, Walters EG. Short-term lower leg growth in 5- to 11-year-old asthmatic children using beclomethasone dipropionate inhalers with chlorofluorocarbon or hydrofluoroalkane propellants: a 9-week, open-label, randomized, crossover, noninferiority study. *Clin Ther* 2011; 33(8): 1069-76.
- 51) Brand PLP, Garcia-Garcia ML, Morison A, Vermeulen JH, Weber HC. Ciclesonide in wheezy preschool children with a positive asthma predictive index or atopy. *Respir Medicine* 2011;105:1588-1595.
- 52) Wolthers OD, Pedersen S. Measures of systemic activity of inhaled glucocorticosteroids in children: a comparison of urine cortisol excretion and knemometry. *Respiratory Medicine* 1995;89:347-349.
- 53) Wolthers OD, Hansen M, Juul A, Nielsen HK, Pedersen S. Knemometry, urine cortisol excretion, and measures of the insulin-like growth factor axis and collagen turnover in children treated with inhaled glucocorticosteroids. *Pediatric Res* 1997;41:44-50.
- 54) Wolthers OD, Sergio F. Systemic activity of inhaled beclomethasone dipropionate: A double blind comparison of volume spacers. *Acta Paediatr* 2012;101(2):159-63.
- 55) Wolthers OD, Ainslee Moore, Sabine Mersmann, Sanjeeva Dissanayake. Knemometry assessment of short-term lower leg growth in children with asthma treated with fluticasone propionate/formoterol combination therapy. Abstract accepted for European Respiratory Society, ERS, September 26-30 2015.
- 56) Wolthers OD. Short term growth and adrenal function in children with asthma treated with inhaled beclomethasone dipropionate hydrofluoroalkane-134a. *Pediatr Allergy Immunol* 2006; 17(8): 613-619.
- 57) Wolthers OD. Systemic activity of inhaled beclomethasone dipropionate hydrofluoroalkane-134a in children with asthma. *Pediatr Asthma Allergy Immunol* 2007; 19(3): 172-179.
- 58) Brambilla G, Ganderton D, Garzia R, Lewis D, Meakin B, Ventura P. Modulation of aerosol clouds produced by pressurised inhalation aerosols. *Int J Pharm* 1999; 186: 53-63.
- 59) Woodcock A, Acerbi D, Poli G. Modulite technology: pharmacodynamic and pharmacokinetic implications. *Respir Med* 2002; 96:suppl D:S9-15.

- Accepted Article
- 60) Wolthers OD, Pedersen S. Short term growth in asthmatic children treated with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; 68: 673-676.
- 61) Chawes BL, Govoni M, Kreiner-Møller E, et al. Systemic exposure to inhaled beclomethasone/formoterol DPI is age and body size dependent. *Respir Med* 2014;108(8):1108-1116.
- 62) Ryrfeldt Å, Andersson P, Edsbäcker S, Töneson M, Davies D, Pauwels R, Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eu J Resp Dis* 1982;63(suppl 122):86-95.
- 63) Cerasoli F. Developing the ideal corticosteroid. *Chest* 2006;130(1):54S-64S.
- 64) Kramer S, Rottier BL, Scholten RJ, Boluyt N. Ciclesonide versus other inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev* 2013; Feb 28;2:CD010352. doi: 10.1002/14651858.CD010352.
- 65) Robroeks CM, van de Kant KD, van Vliet D, et al. Comparison of the anti-inflammatory effects of extra-fine hydroflouroalkane-beclomethasone vs fluticasone dry powder inhaler on exhaled inflammatory markers in childhood asthma. *Ann Allergy Asthma Immunol* 2008;100(6):601-607.
- 66) Pedersen S, Garcia-Garcia ML, Manjra A, Theron I, Engelstätter R. A comparative study of inhaled ciclesonide 160 microg/day and fluticasone propionate 176 microg/day in children with asthma. *Pediatr Pulmonol* 2006;41(10):954-961.
- 67) Vermeulen JH, Gyurkovits K, Rauer H, Engelstätter R. Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir Med* 2007;101(10):2182-2191.
- 68) Kelly HW, Sterneberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367(10):904-912.

Table 1. Median mass aerodynamic diameter (MMAD) (μm) of fine particle size inhaled corticosteroids currently available; see text for references.

Ciclesonide pMDI (Alvesco®):	1.1
Beclometasone dipropionate pMDI (Qvar®; Aerobec®):	1.1
Beclometasone dipropionate+formorol pMDI (Fostair®; Innovair®):	1.1-1.5
Fluticasone furoate+vilanterol trifenatate (Relvar Ellipta®):	2.3
Fluticasone propionate pMDI (Flixotide®):	2.4
Budesonide+formoterol dry powder (DuoResp Spiromax®):	2.5
Fluticasone propionate+formoterol pMDI (Flutiform®):	3.2
Budesonide dry powder (Giona Easyhaler®):	4.0
Budesonide dry powder (Spirocort Turbuhaler®):	4.0
Fluticasone propionate dry powder (Flixotide Discus®):	5.4

Table 2. Pharmacokinetics of extrafine ciclesonide (CIC) and beclomethasone dipropionate (BDP).

(Des-CIC: des-isobutyrol-ciclesonide; 17-BMP: beclomethasone-17-monopropionate.

	CIC	BDP
Active metabolite(s)	des-CIC	17-BMP
Pulmonary deposition	52% of delivered CIC	51% of delivered BDP
Bioavailability of oral deposition	<1%	26%
Bioavailability of pulmonary deposition	100%	100%
Bioavailability of oral and pulmonary deposition	52%	82%
First pass hepatic metabolism	>99%	60%
Pulmonary retention time	>24h	hours*
Esterification	Yes	Yes
Lipophilicity (LogP)	3.2	4.6
Receptor binding affinity	12 times Dexamethasone	13 times Dexamethasone
Half-life at the glucocorticoid receptor	3.5h	2.7h
Plasma protein binding	99%	96%
Detectable in serum	12h**	6h**
Half-life in serum	3.2h**	1.5h**
Plasma clearance	228 L/h	120 L/h

*The information is given in 2); no specific data are available.

**These are the only available data from studies in children (36,38); see text for further references.

Table 3. Summary of knemometry studies of extrafine ciclesonide (CIC) and beclomethasone dipropionate (BDP) in prepubertal children with asthma. All treatment periods were of 2 weeks duration; pMDI's were used with or without a spacer as indicated except *which was administered from the Aerobec® Autohaler®.

	N	Age	Study design	Treatments	Mean LLGR
	Boys/Girls	Range (mean) Years			mm/week
Agertoft 2005 Reference 44) P=0.82	16/8	6-12 (10.0)	CO, R, DB, PL	CIC 40,80,160 µg/day pMDI without a spacer	PL: 0.41 40 µg: 0.43; 80 µg: 0.40; 160 µg: 0.37;
P=0.81					
P=0.49					
Agertoft 2010 Reference 45) P=0.15	13/15	6-12 (10.0)	CO, R, DB, PL	CIC 320 µg/day FP 375 µg/day pMDI with a spacer	PL: 0.43 CIC: 0.30; FP: 0.08;
P<0.001					
Wolthers 2011 Reference 50) P<0.01	51/13	5-11 (8.2)	CO, R, AB	BDP-HFA 200 µg/day BDP-CFC 200 µg/day pMDI with a spacer	Baseline: 0.36 BDP-HFA: 0.27; BDP-CFC: 0.23;
P<0.001					

BDP				HFA was NI to	
Wolthers 2015	38/10	5-11 (8.7)	CO, R, AB	BDP 200 µg/day*	Baseline: 0.37
Reference 55)				FP 200 µg/day	BDP: 0.23;
P=0.01				FP/FORM	FP: 0.42;
P=0.92				200µg/20 µg/day	FP/FORM: 0.38;
P=0.95				pMDI with a spacer	FP/FORM was NI
to FP					

LLGR: lower leg growth rate; CO: cross over; R: randomized; DB: double blind; PL: placebo;

AB: assessor blinded; pMDI: pressurized metered dose inhaler; HFA: hydroflouroalkane;

CFC: chlorofluorocarbon; FP: fluticasone propionate; FORM: formoterol; NI: non inferior

Figure.

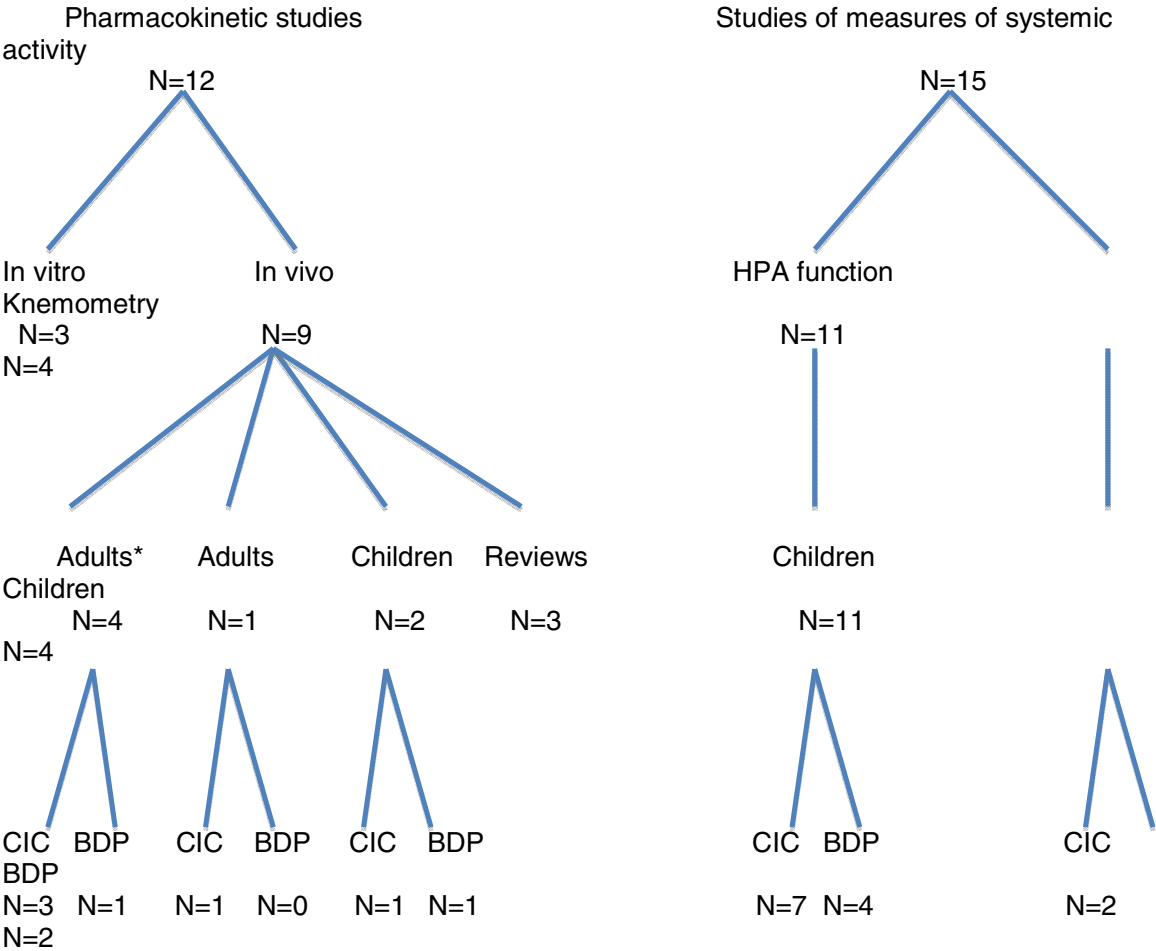


Figure legend

A flowchart of the literature search in pharmacokinetics and systemic activity of extra fine ciclesonide and beclomethasone dipropionate. N: number of studies; *healthy adults, otherwise the studied populations comprised patients with asthma; HPA: hypothalamic-pituitary-adrenal; CIC: ciclesonide; BDP: beclomethasone dipropionate.

Fact box: Abbreviations and definitions

CIC: ciclesonide

Des-CIC: des-ciclesonide

BDP: beclomethasone dipropionate

17-BMP: beclomethasone-17-monopropionate

MMAD: mass median aerodynamic diameter: the diameter of a dose of an inhaled corticosteroid delivered to the 8-stage Andersen Cascade Impactor exclusive of the throat of the impactor

FPP: fine particle fraction: the percentage of a dose of an inhaled corticosteroid delivered to the 8-stage Andersen Cascade Impactor inclusive of the throat with a particle diameter <5 μm

The delivered dose: the amount of a drug that reaches the patient

Pulmonary deposition rate: the amount of an inhaled drug that is deposited in the intrapulmonary airways

Gastro intestinal deposition rate: the amount of an inhaled drug that is deposited in the gastro intestinal tract

Bioavailability: the amount of drug that reaches the systemic circulation

Pulmonary retention time: the time that an inhaled drug resides in the intrapulmonary airways

Receptor binding affinity: the ability of an inhaled corticosteroid to bind to the corticosteroid receptor in the epithelium in the intrapulmonary airways

Protein binding rate: The amount of circulating corticosteroid that is bound to plasma proteins

Knemometry: measurement of the lower leg

LLL: lower leg length

LLGR: lower leg length growth rate

HPA function: Hypothalamic-pituitary-adrenal function