REVIEW ARTICLE

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Safety of Inhaled Budesonide

Clinical Manifestations of Systemic Corticosteroid-Related Adverse Effects

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Abstract

Inhaled corticosteroid (ICS) therapy is central to the long-term management of asthma and is extensively used in the management of chronic obstructive pulmonary disease (COPD). While administration via inhalation limits systemic exposure compared with oral or injected corticosteroids and, therefore, the risk of systemic corticosteroid-related adverse effects, concerns over the long-term safety of ICS persist. The assessment of the long-term effects of ICS therapy requires considerable research effort over years or even decades. Surrogate markers/predictors for

clinical endpoints such as adrenal crisis, reduced final height and fractures have been identified for use in relatively short-term studies. However, the predictive value of such markers remains questionable.

Inhaled budesonide has been available since the early 1980s and there is a considerable evidence base investigating the safety of this agent. To assess the long-term safety of inhaled budesonide therapy in terms of the actual incidence of the clinical endpoints adrenal crisis/insufficiency, reduced final height, fractures and pregnancy complications, we undertook a review of the scientific literature. The external databases BIOSIS, Cochrane Central Register of Controlled Trials, Current Contents, EMBASE, International Pharmaceutical Abstracts and MEDLINE were searched, in addition to AstraZeneca's internal product literature database Planet, up to 29 February 2008. Only original articles of epidemiological studies, national surveys, clinical trials and case reports concerning inhaled budesonide were included.

Eight surveys of adrenal crisis were found. The only survey with specified criteria for diagnosis involved 2912 paediatricians and endocrinologists and revealed 33 patients with adrenal crisis associated with ICS therapy; only one patient used budesonide (in co-treatment with fluticasone propionate). In addition, 14 case reports of adrenal crisis in budesonide-treated patients were found. In only two of these, budesonide was used at recommended doses and in the absence of interacting medication.

Three retrospective studies and one prospective study assessing final height were found. None of them showed any reduced final height in patients receiving inhaled budesonide during childhood or adolescence.

Seventeen epidemiological studies investigating the risk of fractures were found. When adjusting for confounding factors, they did not provide any unequivocal data for an increased fracture risk with budesonide. Four prospective placebo-controlled clinical trials of 2–6 years duration with inhaled budesonide in patients with asthma or COPD were found. None of the studies identified any association between inhaled budesonide and increased risk for fractures.

Four studies using data from the Swedish birth and health registries showed there was no increased risk for congenital malformations, cardiovascular defects, decreased gestational age, birth weight or birth length among infants born to women using inhaled budesonide during pregnancy compared with the general population. This was confirmed by five observational studies in Australia, Canada, Hungary, Japan and the US. Similarly, one randomized clinical trial comparing pregnancy outcomes among asthma patients receiving inhaled budesonide or placebo did not demonstrate any difference in outcome of pregnancy.

In summary, based on 25 years of experience with different doses and in different populations, inhaled budesonide therapy only in very rare cases appears to be associated with an increased risk of adrenal crisis, reduction in final height, increases in the number of fractures or complications during pregnancy.

Asthma affects 300 million people worldwide and the number of annual worldwide deaths from asthma has been estimated at 250 000.[1] The chronic nature of asthma means that the disease requires long-term therapy with anti-inflammatory agents, principally glucocorticosteroids. The long-term use-

fulness of oral corticosteroid therapy has been limited because of the unwanted systemic adverse effects, such as adrenal crisis and other metabolic disorders, suppression of immune function, growth retardation, osteoporotic fractures, weight gain, cataracts and glaucoma. As a result, oral corticosteroids are generally reserved for the short-term treatment of acute asthma exacerbations.

Administration of corticosteroids via inhalation, while associated with local adverse effects such as oropharyngeal candidiasis, can minimize or avoid many of the unwanted systemic adverse effects of oral corticosteroid therapy. As such, international guidelines have for some time recommended inhaled corticosteroid (ICS) therapy as first-line treatment to control the underlying airway inflammation for all patients with persistent asthma.[2,3] However, concerns over the systemic safety of ICS persist.

Documenting the safety of ICS with respect to some of the unwanted systemic adverse effects associated with oral corticosteroid therapy requires an observation time of many years.[4-6] This is reflected by observations that the launch of some ICS with claims of a more favourable therapeutic index than existing ICS[7] were not substantiated in clinical practice,[8-10] underscoring the need for long-term follow-up.

The technical difficulties of measuring the most clinically relevant clinical endpoints, including adrenal crisis, reduced final height and fractures, have led to the development of surrogate markers/predictors in an attempt to reduce the required observation period or the number of participants required to obtain statistically relevant results. For example, cortisol levels and the adrenocorticotropic hormone (ACTH) test have been used as predictors of adrenal crisis, short- to medium-term growth velocity has been used as a predictor of final height, and osteocalcin and bone mineral density measurements have been used as predictors of fracture risk. However, the predictive value of these measurements is variable and studies using them have demonstrated conflicting results.[11]

Inhaled budesonide has been available for the management of asthma since the early 1980s with approximately 15 billion treatment days, and it is currently licensed in more than 90 countries worldwide. As such, a considerable body of evidence has accumulated on the safety profile of the drug with respect to the incidence of systemic corticosteroid-related adverse effects.[12] This review examines the effects of inhaled budesonide with regard to the risk for clinical safety endpoints of adrenal crisis, reduced final height, fractures and pregnancy outcomes. These endpoints were used because they are diagnostically and clinically relevant, are well defined and data are available.

1. Literature Search Methodology

Adrenal crisis, reduced final height, fractures and outcomes of use during pregnancy were selected as clinically relevant measures of the long-term, systemic safety of inhaled budesonide therapy. The external databases BIOSIS, Cochrane Central Register of Controlled Trials, Current Contents, EMBASE, International Pharmaceutical Abstracts and MEDLINE were searched, in addition to AstraZeneca's internal literature database Planet containing published scientific literature references related to AstraZeneca's products, up to 29 February 2008. The content in Planet within the respiratory field can be accessed externally via the medical database on http://www.az-air.com/. The keywords 'budesonide/' or 'budesonide respiratory/' and the free text word 'budesonide' were used. Only original articles of epidemiological studies, national surveys, clinical trials and case reports mentioning inhaled budesonide were included (figure 1). The search prefix 'exp' was used in combination with some of the keywords to include all more specific keywords. It should be noted that this search strategy can be seen as conservative vis-à-vis the safety of budesonide since it may exclude some well designed studies where one of the endpoints (e.g. fractures) did not occur and thus will not be mentioned. As a result of this search, data of other ICS also appeared and were included, but no systematic search for other ICS was carried out.

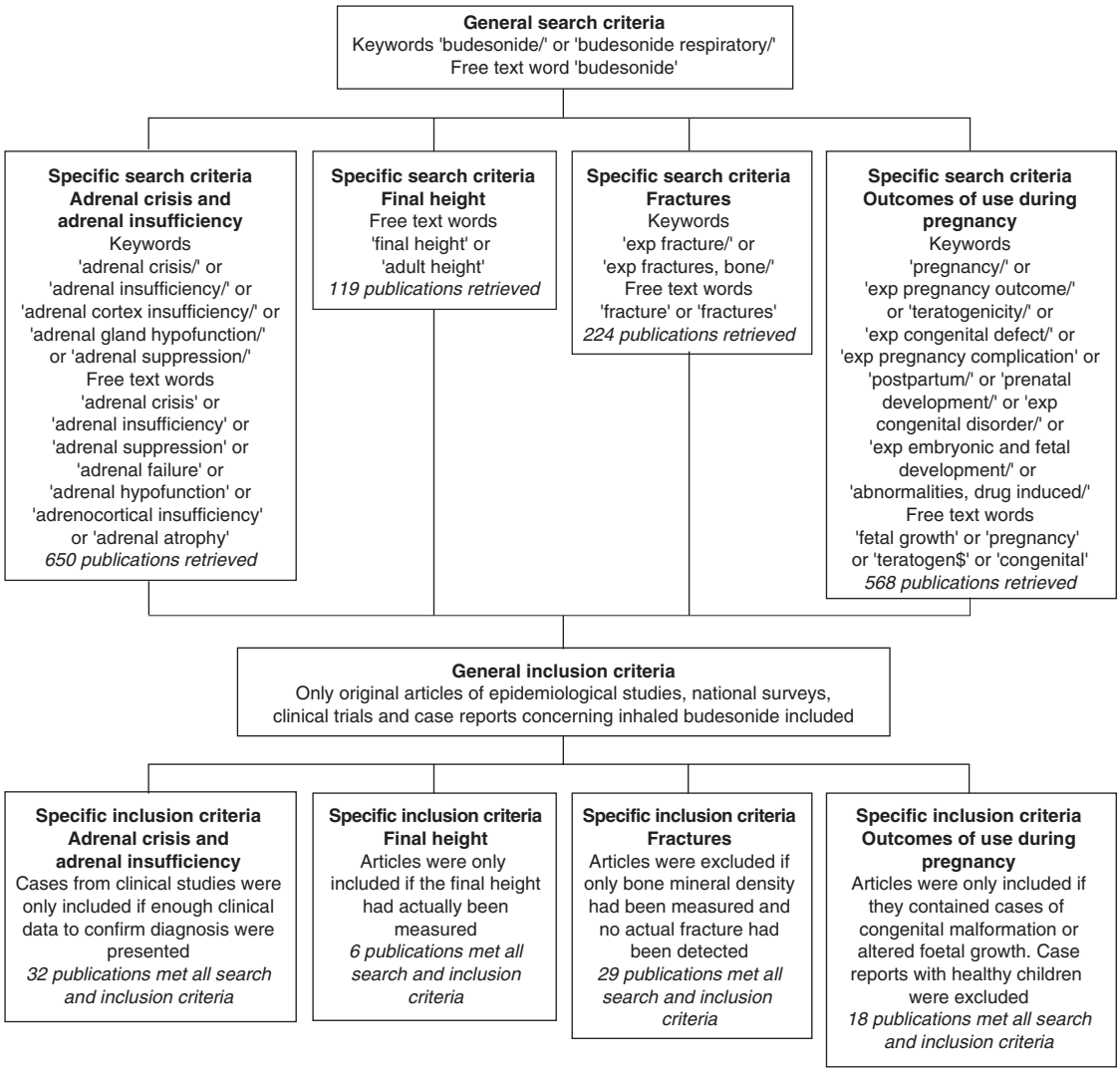

Fig. 1. Literature search strategy.

2. Findings

2.1 Adrenal Crisis and Adrenal Insufficiency

Overt adrenal crisis is a life-threatening phenomenon caused by a lack of cortisol as a result of adrenal gland deterioration, pituitary gland injury or inadequate treatment of adrenal insufficiency. Signs and symptoms are non-specific both in children and adults and include profound weakness, anorexia, fever, abdominal pain, diarrhoea, nausea and vomiting. Hypoglycaemia and decreased level of consciousness and convulsions may also occur and are more frequent in children. Disturbances in salt-water balance are usually not present when the adrenal crisis is caused by exogenous glucocorticoids, resulting in suppression of ACTH release (secondary adrenal insufficiency) since the renin-angiotensin-aldosterone system is intact. During therapy with exogenous steroids, a decrease in the basal

endogenous cortisol production can be observed. This also applies for ICS.[13] From a physiological point of view, this may be regarded as a protective mechanism against hypercortisolism but with a maintained adrenal capacity to respond to medically stressful situations. However, these findings seem to have little impact on the risk for adrenal insufficiency since a decrease in plasma cortisol after steroid treatment is not predictive of clinical adrenal suppression.[14]

The original literature search yielded 650 publications, whereas 32 publications met all inclusion criteria (figure 1). No cases from clinical trials with a confirmed diagnosis according to the criteria defined by Todd et al.[8] (described in section 2.1.2) were found.

2.1.1 Epidemiological Studies

Systematic surveys of the incidence of overt adrenal crisis during ICS therapy are few. Our literature search traced nine survey articles where budesonide was mentioned in the text. The survey by Todd et al.,[8] the only survey that specified criteria for diagnosis and the largest survey of 2912 consultant paediatricians and adult endocrinologists in the UK, revealed 33 patients who met the criteria for adrenal crisis associated with ICS therapy. Of these 33 patients, 30 had used fluticasone propionate, one patient had used both fluticasone propionate and budesonide and two patients had used beclometasone. It should be noted that the majority of patients had used fluticasone propionate at higher doses than licensed for the drug, which may be a consequence of a claimed better benefit/risk ratio compared with other ICS.[7,8]

The remaining eight reports do not specify criteria for diagnosis and do not mention specific symptoms in the patients. A French survey, described with limited information in two separate meeting abstracts,[15,16] reported 46 cases of adrenal insufficiency where 12 of the patients were taking budesonide. In 45 cases, the ICS was used at high doses (>500 μg beclometasone-equivalent per day in children and >1000 μg per day in adults). Furthermore, drug interaction was suspected in 12 of the cases. A Canadian survey identified nine cases of adrenal crisis/insufficiency, all taking fluticasone propionate.[17] In Australia, 10 cases were reported to the Adverse Drug Reactions Advisory Committee.[18] Eight of these patients were taking fluticasone propionate, while the ICS was not mentioned for the other two.

A register study among 94 patients who required acute in-patient care at a single Swedish University hospital for drug-related symptoms during 1997 and 1998 revealed two patients with adrenal insufficiency associated with budesonide therapy and one patient with adrenal insufficiency associated with beclometasone therapy.[19] The basis for diagnosis from symptoms or laboratory investigations is not given but one of the budesonide-treated patients was presented to have hyperglycaemia, a symptom not associated with hypocortisolism.

Of all adverse drug reactions with fatal outcome that had been reported to the UK Committee on Safety of Medicines in 2000, only one case of adrenal insufficiency was associated with ICS (fluticasone propionate) therapy.[20] Of all the suspected adverse drug reactions reported during the use of ICS in children <17 years of age in the Netherlands, only one case of adrenal suppression was reported.[21] This child was treated with inhaled fluticasone propionate and nasal beclometasone.

In 2004, Mortimer and colleagues[22] conducted a case-control study to quantify the association between adrenal insufficiency and ICS exposure. A total of 154 patients newly diagnosed with either adrenal crisis, adrenal insufficiency or Addison's disease, were identified and their exposure to ICS compared with 870 control cases. Thirty-one of these cases occurred in patients that had been prescribed ICS; five of these had been prescribed budesonide. The risk of adrenal insufficiency during ICS therapy (>90 days) was not significantly increased, with an odds ratio (OR) of 1.0 (95% CI 0.4, 2.3) when the data were adjusted for oral corticosteroid exposure. However, the results suggested a dose-related association with the risk of adrenal insufficiency during ICS therapy.

Table I. Case reports of adrenal crisis fulfilling both diagnostic criteria set by Todd et al.[8]

Adrenal function test[a]	Clinical symptoms[b]	Treatment daily dose	Additional treatment daily dose	Reference
Inhaled budesonide in approved doses				
ACTH stimulation 250 μg intravenously, peak cortisol response 85 nmol/L	Varying consciousness, headache, **extreme fatigue**, **vomiting** without diarrhoea or fever, growth retardation, weight gain in a centripetal pattern and moon face Serum potassium 4.3 mmol/L, sodium 127 mmol/L and glucose 5.8 mmol/L	Budesonide 200 μg twice daily Budesonide nasal spray 50 μg twice daily Both stopped 1 wk previously		23
ACTH stimulation test 250 μg, peak cortisol response 418 nmol/L	**Hypoglycaemia** and **convulsion**	Nebulized budesonide 500 μg		24
Inhaled budesonide in higher doses than approved[c]				
Tetracosactide stimulation test 250 μg 1 mo later, peak cortisol response 142 nmol/L	Unresponsive, limp, pale, cyanosed, hypothermic, cushingoid, **hypoglycaemia** with **plasma glucose 0.6 mmol/L**	Nebulized budesonide 4000 μg	Nebulized budesonide 8000 μg decreased to 2000 μg and then increased to 4000 μg 4 mo previously	25
Inhaled budesonide in higher doses than approved[d] plus another corticosteroid administered				
Short tetracosactide stimulation test, peak cortisol response 174 nmol/L	**Lethargy, malaise, nausea, vomiting** and dizziness	Budesonide 2400 μg	Oral prednisone stopped 4 mo before Budesonide decreased from 6400 μg to 3200 μg and then to 2400 μg over a 4-mo period Beclometasone dipropionate nasal spray 200 μg concomitantly	26
Inhaled budesonide plus interacting substance				
Tetracosactide stimulation test 250 μg intravenously, immeasurable cortisol response	(Cystic fibrosis patient) Headache, mood swings, irritability, striae, moon-face, increased facial hair growth, weight gain and Cushing's syndrome **Tiredness** and muscle weakness after treatment was stopped	Budesonide 1600 μg	Itraconazole 800 mg	27
Synacthen 250 μg, peak cortisol response 1.1 μg/dL	Swollen ankles, shortness of breath, **fatigue**, **lethargy**, leg weakness and Cushingoid	Budesonide 1200 μg Increased to budesonide 1600 μg	Itraconazole 400 mg	28
Short Synacthen test, peak cortisol response 212 nmol/L	Presyncope, **fatigue**, abdominal distension, moonface, hypertension, **lethargy** and weakness	Fluticasone propionate 1000 μg (switched from budesonide 400 μg)	Ritonavir 200 mg	29

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Table I. Contd

Adrenal function test[a]	Clinical symptoms[b]	Treatment daily dose	Additional treatment daily dose	Reference
Inhaled budesonide stopped >3 mo before				
Tetracosactide stimulation test 1 μg, peak cortisol response 138 nmol/L	**Fatigue**	Fluticasone propionate 250 μg	Nebulized budesonide 500 μg stopped 2 y before Fluticasone propionate 1000 μg decreased to 500 μg 1 y before and then to 250 μg 6 mo before	30
Standard dose ACTH Synacthen test, peak cortisol response 30 nmol/L	Drowsy, disoriented, headache, **hypoglycaemia** with **plasma glucose 0.7 mmol/L**	Fluticasone propionate 500 μg	Budesonide 400 μg stopped 4 mo before	31
Short tetracosactide stimulation test 250 μg intramuscularly, cortisol increase from baseline 25 nmol/L	**Vomiting, hypoglycaemia** with **plasma glucose 1.3 mmol/L**	Fluticasone propionate 1000–2000 μg	Budesonide 1600 μg stopped 5 mo before	32 (in Todd survey)
Short Synacthen stimulation test 250 μg, cortisol response 108 nmol/L	**Hypoglycaemia** with **blood glucose 1.3 mmol/L, vomiting, abdominal pain**, drowsiness, fever, rhinorrhoea, **fatigue** and hyponatraemic with sodium 130 mmol/L	Fluticasone propionate 1500 μg	Oral prednisolone stopped 8 mo before Nebulized budesonide 1000 μg stopped 3 wk before	33
Inhaled budesonide started after adrenal crisis already had appeared with another corticosteroid				
1. Low-dose short tetracosactide test, peak cortisol response 270 nmol/L	1. Growth retardation 2. **Nausea, vomiting, severe fatigue, upper abdominal pain**	1. Fluticasone propionate 1000 μg 2. Budesonide 800 μg		34 (in Todd survey)
1. Short tetracosactide stimulation test 250 μg intramuscularly, peak cortisol response 256 nmol/L	1. **Fatigue**, sweating and decreased exercise tolerance 2. **Nausea, vomiting, abdominal pain, fatigue** and **dizziness**	1. Fluticasone propionate 1000–2000 μg 2. Budesonide 800 μg		32 (in Todd survey)
Blood cortisol 1.1 μg/dL	**Fatigue**, myopathy	Fluticasone propionate 1000 μg	Improved after changing to budesonide 400 μg and sodium cromoglicate 30 mg	35

a Normal cortisol response is above 500 nmol/L or 18.2 μg/dL.

b Clinical symptoms defined by Todd et al.[8] are in bold.

c Nebulized budesonide is approved up to 4000 μg daily for adults and elderly and 2000 μg for children ≥6 mo of age. The patient receiving 4000 μg nebulized budesonide was a 21-mo-old boy.[25]

d Inhaled budesonide is approved up to 1600 μg daily for adults and elderly (2400 μg daily in Australia and Canada) and 800 μg daily for children ≥6 y of age. The patient receiving between 2400 and 6400 μg was a 38-y-old man.[26]

ACTH = adrenocorticotropic hormone.

2.1.2 Case Reports of Adrenal Crisis

In the survey by Todd et al.,[8] diagnosis of acute adrenal crisis required both of the following criteria:

1. At least one of the following symptoms or signs: lethargy, nausea or vomiting, diarrhoea, hypotension, abdominal pain, unexplained hypoglycaemia, convulsion.

2. At least one of the following indications of abnormal hypothalamic-pituitary-adrenal axis function: acute presentation of serum cortisol response to critical illness <500 nmol/L, peak cortisol response <500 nmol/L to a short Synacthen stimulation test (tetracosactide 250 μg intramuscularly) or a failure to increase >200 nmol/L from baseline, peak cortisol response <500 nmol/L to glucagon stimulation test (glucagon 500 μg intramuscularly).

Fourteen cases of adrenal crisis fulfilling these criteria in patients treated with inhaled budesonide have been described (table I). In two of these cases, budesonide was under current use at recommended doses and in the absence of treatment with interacting medications. One child was treated with inhaled budesonide 200 μg twice a day and nasal budesonide 50 μg twice a day.[23] In addition, one child with multiple malformations had been treated with nebulized budesonide 500 μg per day and at 7 years of age he was diagnosed with adrenal insufficiency due to isolated ACTH deficiency.[24] The conclusion of the authors was that the patient had a pituitary or hypothalamic defect.

Two patients were treated with budesonide in a higher dose than the maximal recommended dose. Inhaled budesonide is approved up to 1600 μg daily for adults and the elderly (2400 μg daily in Australia and Canada) and 800 μg daily for children ≥6 years of age. Nebulized budesonide is approved up to 4000 μg daily for adults and elderly and 2000 μg for children ≥6 months. One patient, a 21-month-old child, was treated with nebulized budesonide 4000 μg/day[25] and one patient was treated with beclometasone nasal spray concomitantly with 2400–3200 μg of inhaled budesonide.[26] Three cases occurred in patients who were concomitantly treated with itraconazole[27,28] or ritonavir,[29] substances that inhibit cytochrome P450 (CYP) 3A4 activity resulting in increased exposure to budesonide. One of them was a patient with cystic fibrosis.[27] In four cases, budesonide treatment had been stopped more than 3 months before adrenal crisis was identified (range: 4 months–2 years); therefore, it is unlikely that budesonide was causally linked to the adrenal crisis. All patients were under treatment with inhaled fluticasone propionate at the time of diagnosis.[30-33] Furthermore, three patients with already apparent adrenal insufficiency were switched from fluticasone propionate to budesonide treatment.[32,34,35]

2.1.3 Case Reports of Adrenal Insufficiency

Nineteen case reports of adrenal insufficiency in patients treated with inhaled budesonide were found where no dynamic test had been performed (or plasma cortisol measured at an occasion of severe stress), or none of the defined clinical symptoms of adrenal crisis were described (table II). Five patients were treated with inhaled budesonide[31,36,37] as the only corticosteroid. One of these was a 7-year-old child treated with a higher daily dose (1000 μg) than recommended.[37] Three cases occurred in cystic fibrosis patients who were concomitantly treated with itraconazole[38-40] or clarithromycin.[39] In nine cases, budesonide had been stopped more than 3 months before adrenal insufficiency occurred (range: 5 months–3 years),[30,41-43] and in all these cases the treatment had been changed to inhaled fluticasone propionate prior to diagnosis. In two other cases, the symptoms improved after switching from fluticasone propionate to budesonide.[44,45]

2.1.4 Summary of Adrenal Crisis and Adrenal Insufficiency

In summary, overt adrenal crisis appears to be extremely rare with inhaled budesonide in approved doses.

2.2 Final Height

It is now well recognized that even small doses of corticosteroids, including ICS, have a temporary effect on short- and medium-term growth velocity. However, until recently, whether this effect translates into a reduction in final height has remained unanswered.

Table II. Case reports of adrenal insufficiencty not fulfilling both diagnostic criteria set by Todd et al.[8]

Adrenal function test[a]	Clinical symptoms[b]	Treatment daily dose	Additional treatment daily dose	References
Inhaled budesonide in approved doses				
No test	Hyperglycaemia and Cushingoid	Budesonide 2000 μg		36
No test	**Fatigue, nausea** and **diarrhoea**	Budesonide 400 μg		37
Plasma cortisol 162 nmol/L at 0900h	Poor growth in height and weight for 2 y	Budesonide 400 μg		31
Plasma cortisol <20 nmol/L at 0900h	Poor growth in height and hirsutism for 6 mo	Budesonide 400 μg		31
Inhaled budesonide in higher doses than approved[c]				
Serum cortisol 10 nmol/L	Growth retardation, centripetal weight gain and a Cushingoid moonface	Budesonide 1000 μg		37
Inhaled budesonide plus interacting substance				
Immeasurable cortisol	(Cystic fibrosis patient) Moon-face, weight gain	Budesonide 400 μg	Clarithromycin 1000 mg	39
Serum cortisol <3 μg/L	(Cystic fibrosis patient) Moon face, swollen abdomen, weight gain	Budesonide 400 μg	Itraconazole 200 mg	38,39
No test	(Cystic fibrosis patient)	Budesonide	Itraconazole high dose	40
Inhaled budesonide stopped more than 3 mo previously				
Insulin tolerance test, peak cortisol response <30 nmol/L	Growth rate reduced	Fluticasone propionate 1500 μg	Nebulized budesonide 2000 μg stopped >1 y before	43
Insulin tolerance test, peak cortisol response <30 nmol/L	Growth rate reduced	Fluticasone propionate 2250 μg	Budesonide 800 μg stopped 3 y before	43
Synacthen 250 μg test, peak cortisol response <30 nmol/L	Growth rate reduced	Fluticasone propionate 1500 μg	Budesonide 800 μg stopped >2 y before	43
Low-dose Synacthen 0.5 μg test, peak cortisol response 167 nmol/L	Growth rate reduced	Fluticasone propionate 1000 μg	Budesonide 1800 μg stopped >2 y before Beclometasone nasal spray 200 μg	43
Synacthen 250 μg test, peak cortisol response 199 nmol/L	Growth rate reduced	Fluticasone propionate 1000 μg	Budesonide 1800 μg stopped >1 y before	43

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Table II. Contd

Adrenal function test[a]	Clinical symptoms[b]	Treatment daily dose	Additional treatment daily dose	References
No test	**Vomiting**, **fatigue**, fever Serum sodium 131 mmol/L	Fluticasone propionate 750 μg	Fluticasone 1500 μg previously Nebulized budesonide 4000 μg stopped >1 y before	30
Serum cortisol 15 nmol/L	Excessive weight gain	Fluticasone propionate 500 μg	Budesonide 800 μg stopped 7 mo before	41
ACTH stimulation test, peak cortisol response 85 nmol/L	Round face, growth retardation	Fluticasone propionate 250 μg	Beclometasone dipropionate 400 μg decreased to 200 μg Budesonide 800 μg decreased to 400 μg stopped 5 mo before	41
ACTH stimulation test, peak cortisol response >20 μg/dL, i.e. normal value	Weakness and **fatigue**	Fluticasone propionate 880 μg	Budesonide 800 μg stopped 7 mo before Fluticasone increased from 176 μg to 440 μg 4 mo before and then to 880 μg 3 mo before Oral prednisone stopped 3 mo before Mometasone nasal spray concomitantly	42
Inhaled budesonide started after adrenal crisis already had appeared with another corticosteroid				
Serum cortisol 20 nmol/L at 0900h	Proximal myopathy, osteopenia, hypertension, depressive psychosis and Cushingoid appearance	Fluticasone propionate 2000 μg	Improved after changing to budesonide 800 μg	44
Cortisol <1 μg/dL	Cushingoid face and steroid acne	Oral prednisone and intranasal triamcinolone stopped 7 mo before Fluticasone propionate 440 μg	Improved after changing to budesonide	45

a Normal cortisol response is above 500 nmol/L or 18.2 μg/dL.

b Clinical symptoms defined by Todd et al.[8] are in bold.

c Inhaled budesonide is approved up to 1600 μg daily for adults and elderly (2400 μg daily in Australia and Canada) and 800 μg daily for children ≥6 y of age. The patient receiving 1000 μg was a 7-y-old girl.[37]

ACTH = adrenocorticotropic hormone.

The original literature search yielded 119 publications, whereas 6 publications met all inclusion criteria (figure 1). No case reports were found.

2.2.1 Epidemiological Studies

Asthma itself can have an impact on growth: the height of 18-year-old Swedish conscripts with and without asthma was analysed in a long-term retrospective study in 1983, 1986, 1993 and 1996.[46] The cohort with asthma was, on average, 0.7 cm shorter than the non-asthmatic cohort. During the study period, inhaled budesonide was introduced to the Swedish market and showed no negative influence on height. In fact, the mean height difference between conscripts with severe asthma and conscripts without asthma decreased from 2.3 cm in 1983 to 1.2 cm in 1993 and in 1996, suggesting that improved asthma treatment had a positive effect on their growth.

Larsson and co-workers[47] compared the final height of asthmatic individuals with that of an age-matched control group of healthy volunteers. Among the 152 asthmatic patients assessed, both men and women achieved a higher mean final height than the calculated mean target height. Importantly, there was no difference in final height between asthmatic patients treated with ICS (principally budesonide) during childhood/adolescence and healthy volunteers and neither the age at the start of treatment with ICS nor the cumulative dose of budesonide affected the final height. These data indicate that therapy with inhaled budesonide given during childhood/adolescence is not likely to affect final height.

A small retrospective study assessed adult height in 42 patients treated with ICS starting at a mean age of 13.3 years (range 5–18 years) compared with 43 controls with asthma but not treated with ICS during childhood.[48] The target height was achieved in both groups but surpassed in the non-ICS group, which contained patients with mild asthma and had older patients compared with the ICS group. The effect of budesonide on adult height cannot be evaluated from this study since only one patient was treated with budesonide as the only ICS.

2.2.2 Controlled Clinical Trials

A single long-term prospective study assessed final adult height in children receiving inhaled budesonide.[49] The adult height of children receiving inhaled budesonide at a mean daily dose of 412 μg for 3–13 years was compared with the adult height of asthmatic children not receiving any ICS and healthy siblings of patients in the budesonide group.[49] All three groups of children reached their target adult height (figure 2). Neither the duration of budesonide treatment nor the cumulative dose of budesonide affected final adult height. However, during the first 2 years of budesonide treatment, the growth rate was lower than during the run-in period. These authors have continued to follow prospectively this group of children and recently presented data on final height and time of achievement of final height.[50,51] Children had been treated for asthma for 1.8–19.2 years with a mean inhaled budesonide dose of 410 μg/day. Final height was considered 'final' when the patient's height did not increase by >0.5 cm over a 2-year period. The authors found that in the 75 girls and 141 boys where final height had been reached, the mean final adult height was normal compared with predicted values and healthy siblings. However, the time of achievement of final adult height was delayed. The authors went on to point out that studies assuming that adult height in ICS-treated asthmatic patients is reached at the same age as healthy children will underestimate the adult height of the asthmatic patients.[50] This study is still

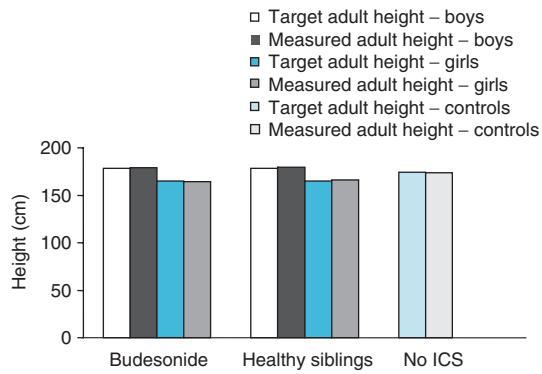

Fig. 2. Final adult height among asthmatic patients treated with budesonide during childhood/adolescence.[49] **ICS** = inhaled corticosteroid.

ongoing since final height has not yet been reached in 47 patients.

2.2.3 Summary of Final Height

In summary, studies with the relevant endpoint final height clearly indicate that patients treated with inhaled budesonide attain their expected final height.

2.3 Fractures

Osteoporosis and associated low-energetic fractures are well known clinical complications in a variety of chronic medical conditions treated with long-term oral corticosteroids including asthma, rheumatic diseases and gastrointestinal diseases. Indeed, up to half of all patients receiving extended oral corticosteroid therapy will experience fractures.[52] Fractures such as spontaneous lumbar compression fractures or an increased risk of hip fractures are seen as clinical manifestations of osteoporosis, and the potential for such effects with ICS has been of considerable clinical concern.

The original literature search yielded 224 publications, whereas 29 publications met all inclusion criteria (figure 1). A summary of studies retrieved from the literature on increased risk of fractures and a potential association with budesonide is presented in table III, and details from some important studies are further outlined below. In addition to the list of studies in table III, a number of sporadic case reports regarding budesonide and fractures have been published as part of uncontrolled clinical trials.[53-57]

2.3.1 Epidemiological Studies

Epidemiological studies provide some contradictory results regarding the increased risk of fractures with ICS including budesonide (table III). As referred to in the discussion, there are several explanations for this, confounding by underlying disease being the most important. Many studies do not demonstrate any increased risk for ICS in general, or budesonide in particular.[59,64,66,67,69,70,72,73] Regarding studies indicating an increased risk of fractures, the study of Hubbard et al.[71] is an example. This was a prescription-based event study recording all fractures in a cohort of 1671 patients with 'airflow obstruction' and at the start of the study, the mean age was 80.6 years. ICS exposure was described as mean daily dose and all ICS were assumed to be equipotent. The crude incidence of fractures was 21.7 per 1000 person-years in unexposed patients and 25.7 in exposed. A statistically increased risk adjusted for confounders was found in the highest dose group, who received >601 μg/day (table III). Among all exposed patients, 109 (11%) received budesonide as the only ICS, although it is unclear how many of these who belonged to the highest dose interval (>601 μg/day) that was associated with an increased risk of fractures. Another nested case-control study in patients with chronic obstructive pulmonary disease (COPD) by the same group involved 1235 patients >40 years of age, 16% of whom were treated with budesonide, and 4598 controls.[68] Adjusted for age, sex, predicted forced expiratory volume in 1 second, general practice and oral corticosteroid use, an increased risk for fractures was only found in the highest ICS dose ≥1600 μg (OR = 1.74; 95% CI 1.00, 3.01). This group consisted of 28 patients, although it is not known if any of these received budesonide. Of the other case-control studies that have shown an increased risk of fractures with ICS, one study is only published as a meeting abstract with scarce data[58] and two studies have recalculated all ICS to prednisolone equivalents and only showed increased fracture risk with high doses (prednisolone ≥7.5 mg)[60,63] [table III]. However, when adjusting the data[60] for disease severity, ICS treatment no longer showed any association with an increased risk of fractures.[61]

2.3.2 Controlled Clinical Trials

The results of prospective placebo-controlled clinical trials with budesonide in patients with asthma or COPD have not identified any association between inhaled budesonide and increased fracture rate (table III). In EUROSCOP (The European Respiratory Society study on chronic obstructive pulmonary disease), a sub-population of 653 COPD patients randomized to budesonide (800 μg/day) or placebo underwent x-ray of the spine at baseline and end of treatment. Only five patients with new frac-

Table III. Studies evaluating the effect of inhaled corticosteroids (ICS) on fracture rate

Design	Underlying disease (asthma or COPD/ outcome)	Patients/daily dose	Results		References
			conclusion	RR or OR (95% CI)/no. of patients with fracture (%)	
Epidemiological and retrospective studies					
Case-control study	COPD/non-vertebral fractures	GPRD Adults (50–85 y) Cases non-vertebral fractures n = 2808 Controls n = 8453	Risk of non-vertebral fractures increased with beclometasone and budesonide but not with fluticasone propionate		58
			Beclometasone Budesonide Fluticasone propionate	OR = 1.46 (1.26, 1.69) OR = 1.41 (1.10, 1.79) OR = 0.78 (0.55, 1.09)	
Case-control study	Not defined/fractures	GPRD Adults (over 18 y) Cases ICS n = 170 818 Controls, bronchodilators n = 108 786	Relative to bronchodilators ICS treatment did not increase the risk of vertebral, non-vertebral and hip fractures		59
		Controls other n = 170 818 ICS (beclometasone 86%, budesonide 11% and fluticasone propionate 2%)	Vertebral fractures Non-vertebral fractures Hip fractures	RR = 0.90 (0.71, 1.14) RR = 1.00 (0.94, 1.06) RR = 1.20 (0.99, 1.45)	
Case-control study	Not defined/fractures	Cases fractures n = 124 655 Controls n = 373 962	Risk of fractures increased with high doses of ICS (≥7.5 mg prednisolone equivalents per day)	OR = 1.17 (1.00, 1.38)	60
Case-control study	Not defined/fractures	Cases fractures n = 124 655 Controls n = 373 962 ICS (budesonide and fluticasone propionate)	ICS treatment did not increase the risk of fractures after adjustment for disease severity – risk associated with asthma, COPD, emphysema or other chronic lung diseases	OR = 0.93 (0.87, 0.99)	61
			Hip fractures Forearm fractures Spine fractures	OR = 0.72 (0.60, 0.86) OR = 0.92 (0.78, 1.08) OR = 0.61 (0.44, 0.84)	
Case-control study	Not defined/hip fractures	GPRD Cases hip fractures n = 16 341 Controls n = 29 889 ICS (beclometasone 84%, budesonide 14% and fluticasone propionate 2%)	Risk of hip fractures increased with ICS The fracture risk was dose related	OR = 1.19 (1.10, 1.28) when adjusted for use of oral cortciosteroids	62
Case-control study	Not defined/hip fractures	Adults (over 18 y) Cases hip fractures n = 6660 Controls n = 33 272	Risk of hip fractures increased with high doses of ICS (≥7.5 mg prednisolone equivalents per day)	OR = 1.36 (1.19, 1.56)	63

Continued next page

Table III. Contd

Design	Underlying disease (asthma or COPD/ outcome)	Patients/daily dose	Results		References
			conclusion	RR or OR (95% CI)/no. of patients with fracture (%)	
Case-control study	Not defined/hip/ femur fractures	Adults (over 18 y) Cases hip/femur fractures n = 6763 Controls n = 26 341 ICS (beclometasone, budesonide and fluticasone propionate)	ICS treatment did not increase the risk of hip/femur fractures after adjustment for disease severity	OR = 1.08 (0.91, 1.27)	64
Case-control study	Not defined/ osteoporotic fractures	GPRD Adults (over 18 y) Osteoporotic fractures n = 108 754 Controls n = 108 754 ICS (beclometasone, budesonide and fluticasone propionate)	ICS treatment did not increase the risk of osteoporotic fractures after adjustment for disease severity – risk associated with asthma or COPD not ICS The fracture risk was dose related Beclometaone equivalents:		65
			1–400 μg ≥1600 μg	OR = 1.04 (0.95, 1.14) OR = 1.19 (1.01, 1.41)	
Nested case-control study	Asthma or COPD or neither/bone fractures	GPRD Children and adolescents (5–17 y) Cases bone fractures n = 3744 Controls n = 21 757 ICS (beclomethasone 76%, budesonide 22% and fluticasone propionate 2%)	ICS treatment did not increase the risk of fractures in children or adolescents, when adjusted for use of other anti-asthmatic drugs (β-agonists, theophyline, anticholinergics, leukotriene antagonists, mast cell stabilizers or ketotifen)	OR = 1.15 (0.83, 1.60)	66
Nested case-control study	Asthma or COPD/ non-vertebral	Adults (over 40 y) Cases non-vertebral fractures n = 1722	ICS treatment did not increase the risk of non-vertebral fractures		67
	fractures	Controls n = 17 220 ICS (beclometasone, budesonide, flunisolide, fluticasone propionate and triamcinolone)	All ICS Fluticasone propionate Other ICS	OR = 1.05 (0.89, 1.24) OR = 1.13 (0.90, 1.40) OR = 0.97 (0.78, 1.21)	
Nested case-control study	COPD/fractures	Adults (over 40 y) Cases fractures n = 1235	Risk of fractures increased with high doses of ICS		68
		Controls n = 4598 ICS (beclometasone 66%, budesonide 16%, fluticasone propionate 18%)	≥1600 μg	OR = 1.80 (1.04, 3.11)	

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Table III. Contd

Design	Underlying disease (asthma or COPD/ outcome)	Patients/daily dose	Results		References
			conclusion	RR or OR (95% CI)/no. of patients with fracture (%)	
Nested case-control study	Not defined/new fractures	Elderly (over 65 y) Cases new fractures n = 9624 Controls n = 191 622 ICS (beclometasone 63%, budesonide 19%, fluticasone propionate 17%)	ICS treatment did not increase the rate of fractures, when adjusted for use of oral corticosteroids and other drugs (β-agonists, ipratropium bromide, theophylline, diuretics, NSAIDs, estrogens, thyroid hormones, cardiovascular drugs or rheumatic drugs)	RR = 0.97 (0.92, 1.03)	69
Nested case-control study	Not defined/new fractures	GPRD Children and adolescents (4–17 y) prescribed a corticosteroid Cases ICS n = 97 387 Controls bronchodilators n = 70 984 Controls n = 345 758 ICS (beclometasone, budesonide and fluticasone propionate)	ICS treatment did not increase the risk of fractures after adjustment for asthma severity – risk associated with illness not ICS	OR = 1.03 (0.93, 1.15)	70
Cohort study	Asthma or COPD/ new fractures	Elderly (mean age 80.6 y) ICS n = 982 Controls n = 689	Risk of hip fractures increased in patients taking ICS The fracture risk was dose related		71
		ICS (beclomethasone 74%, budesonide 10%, fluticasone 3% and more than one 13%)	ICS >601 μg	RR = 2.53 (1.65, 3.89)	
Retrospective cohort study	Not defined/hip fractures	Elderly women (over 65 y) ICS n = 24 648 Systemic corticosteroids n = 27 751 Estrogen n = 28 119 Proton pump inhibitors n = 34 855 ICS (beclometasone, budesonide, flunisolide and fluticasone propionate)	Relative to proton pump inhibitors ICS treatment did not increase the risk of hip fractures	RR = 0.92 (0.75, 1.12)	72
Cross-sectional cohort study	Asthma, COPD or fibrosing alveolitis/ vertebral fractures	Adults (over 50 y) Oral corticosteroids n = 117 ICS (beclometasone, budesonide and fluticasone propionate)	ICS treatment did not increase the risk of vertebral fractures	OR = 1.4 (0.34, 6.1)	73

Continued next page

Table III. Contd

Design	Underlying disease (asthma or COPD/ outcome)	Patients/daily dose	Results		References
			conclusion	RR or OR (95% CI)/no. of patients with fracture (%)	
Cross-sectional cohort study	Pollen-allergy/bone fractures	Postmenopausal women ICS n = 12 ICS and H_1R antagonist n = 17 H_1R antagonist n = 53 No treatment n = 43 Controls (non-allergic women) n = 100 ICS (budesonide, fluticasone propionate and mometasone)	Allergic women had an increased risk of fractures Risk of fractures increased in women taking ICS		74
Randomized controlled clinical trials					
2-y study x-Ray at baseline	Asthma/vertebral fractures	Adults (20–60 y) Budesonide (400 μg) n = 87	Inhaled budesonide had no effect on fracture rate in asthma patients		75
and end of treatment		Beclometasone (500 μg) n = 74 No steroid n = 78	Budesonide	1/87 (1.1%)	
3-y double-blind study (EUROSCOP) x-Ray at baseline and	COPD/vertebral fractures	Adults (30–65 y) Budesonide (800 μg) n = 322	Inhaled budesonide had no significant effect on fracture rate in COPD patients		76,77
end of treatment		Placebo n = 331	Budesonide Placebo	5/322 (1.55%) 3/331 (0.91%)	
3-y double-blind study (START) Spontaneous	Asthma/new fractures	(5–66 y) Budesonide (children 200 μg and adolescents and adults 400 μg)	Inhaled budesonide had no significant effect on fracture rate in asthma patients		78,79
reporting and patients' responses to standard questioning		n = 3630 Placebo n = 3591	Budesonide	61/3630 (1.7%)	
			Placebo	78/3591 (2.2%)	
3-y double-blind study (START) Spontaneous	Asthma/new fractures	Children (5–10 y) Budesonide (200 μg) n = 1004 Placebo n = 977	Inhaled budesonide had no significant effect on fracture rate in asthmatic children		80[a]
reporting and patients' responses to standard questioning			Budesonide Placebo	10/1004 (1.0%) 8/977 (0.82%)	
4- to 6-y double-blind study (CAMP)	Asthma/new fractures	Children (5–12 y) Budesonide (400 μg) n = 311 Nedocromil (8 mg) n = 312	Inhaled budesonide had no significant effect on fracture rate in asthmatic children		81
		Placebo n = 418	Budesonide Nedocromil Placebo	5.7/100 person-y 4.1/100 person-y 5.1/100 person-y	

a Subset of the data in Pedersen et al.[78] and Sheffer et al.[79]

CAMP = The Childhood Asthma Management Program; **COPD** = chronic obstructive pulmonary disease; **EUROSCOP** = The European Respiratory Society study on chronic obstructive pulmonary disease; **GPRD** = General Practice Research Database in the United Kingdom; **H_1R antagonist** = H_1 histamine receptor antagonist; **OR** = odds ratio; **RR** = relative risk; **START** = The inhaled Steroid Treatment As Regular Therapy in early asthma.

tures were reported during 3 years of follow-up in the budesonide group compared with three patients in the placebo group (p = 0.5).[76,77] Similarly, low rates of new fracture were reported among 7221 patients with asthma who took part in the inhaled START (Steroid Treatment As Regular Therapy in early asthma) study with budesonide (200–400 μg/day).[78,79] New fractures were reported by 61 of 3630 (1.7%) patients randomized to budesonide and 78 of 3591 (2.2%) patients randomized to placebo,[78] and new fractures as serious adverse events were reported by 19 of 3630 (0.52%) patients randomized to budesonide and 22 of 3591 (0.61%) patients randomized to placebo[79] during 3 years of follow-up. Finally, in a comparative study of the effect of 2 years' treatment with ICS (budesonide or beclometasone propionate) or non-corticosteroid treatment, only one patient reported a fracture during the study period.[75]

2.3.3 Summary of Fractures

In summary, an increased risk of fractures with long-term ICS use has been suggested by some epidemiological studies while others show contrary results. No increased risk has been shown in controlled clinical trials with inhaled budesonide.

2.4 Pregnancy

Poorly controlled asthma can lead to significant and even life-threatening complications for both mother and fetus.[82,83] Asthma has been associated with preterm delivery, pre-eclampsia and an increased risk of caesarean section.[84-86] In 2005, Murphy and co-workers[82] reported that exacerbations of asthma during pregnancy were associated with a poor outcome for male fetuses including a significantly increased risk of low birth weight (p = 0.03). Thus, there is a definite medical need for appropriate asthma medications that are safe for use during pregnancy.

The original literature search yielded 568 publications, whereas 18 publications met all inclusion criteria (figure 1).

2.4.1 Epidemiological Studies

Four studies using data from the Swedish birth and health registries showed there was no adverse effect of budesonide therapy during pregnancy for a range of outcomes. Källén and co-workers[87] examined data on congenital malformations among 2014 babies born to mothers who had used budesonide during pregnancy and found the incidence rate to be comparable with that of the general population (3.8% vs 3.5%). A further case-control study found no increase in the risk of cardiovascular defects among infants whose mothers used budesonide as an inhaled anti-asthmatic medication during pregnancy.[88] In 2003, Norjavaara and Gerhardsson de Verdier[89] examined gestational age, birth weight and length, and the rate of stillbirth and multiple births and found no increased risk among 2968 women who used inhaled budesonide during early pregnancy. Recently, Källén and Otterblad Olausson[90] updated the analysis of congenital malformations among 10 013 infants exposed to budesonide. There were still no significant increased risk of any malformations (OR = 1.04; 95% CI 0.95, 1.14), cardiac defects (OR = 1.13; 0.96, 1.33), median cleft palate (OR = 1.57; 0.96, 2.57) or anal atresia (OR = 1.91; 0.95, 3.42).[90]

One study used three Canadian databases of prescribed medications, births and stillbirths, and hospitalizations and medical diagnosis to investigate the risk of congenital malformations among babies born to mothers who had used ICS (63% beclometasone, 19% fluticasone propionate and 17% budesonide) during the first trimester of pregnancy.[91] Within the cohort, 418 babies were identified with at least one malformation. There was no association between congenital malformations and the use of ICS during the first trimester of pregnancy, irrespective of dose: OR = 0.77 (95% CI 0.53, 1.13) for 1–500 μg beclometasone equivalents per day, OR = 0.41 (95% CI 0.19, 0.92) for 501–1000 μg and OR 1.00 (95% CI 0.42, 2.36) for >1000 μg.

In the American population-based case-control study 'National Birth Defects Prevention Study', mothers of 1141 infants with cleft lip, 628 infants with cleft palate and 4143 controls were telephone

interviewed.[92] Three mothers of infants with cleft lip had used budesonide from 4 weeks before through 12 weeks after conception (RR = 2.8, 95% CI 0.6, 12.3), and two mothers of infants with cleft palate (RR = 3.3, 95% CI 0.6, 17.9) compared with four controls.

The risk of congenital abnormalities has been assessed in a case-control study using the Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996.[93] Among asthmatic mothers giving birth to children with congenital abnormalities, 1.2% had taken inhaled budesonide, while among asthmatic mothers giving birth to healthy children 1.5% had taken inhaled budesonide (OR = 0.8; 95% CI 0.3, 2.2).

Two small prospective observational studies with a total of 834 pregnant asthmatic women treated with ICS showed no increased risk of low birth weight or congenital malformations.[94,95] Inhaled budesonide was used by 17% of the mothers with asthma; the other ICS were fluticasone propionate, beclometasone, triamcinolone and flunisolide. It is stated that the incidence of small for gestational age varied between the different ICS (1.4% for budesonide, 7.0% for fluticasone propionate and 7.5% for beclometasone) even though they were similar to those of controls without asthma and asthmatic patients treated with β_2-adrenergic receptor agonists only.[95] However, no frequencies were presented for these groups.

Another small prospective observational study investigated the birth weight in children born to a total of 92 pregnant women with asthma treated with ICS.[96-98] Asthmatic women not treated with ICS gave birth to children with significantly lower birth weights ($p < 0.05$) than asthmatic women treated with ICS and non-asthmatic women.[96,97] Treatment with inhaled budesonide was associated with normal birth weight compared with the non-asthmatic control group.[98]

One retrospective study of 11 358 pregnant women in Japan, of whom 592 had asthma, investigated the safety of ICS during pregnancy.[83] Of these women with asthma, 118 received ICS (beclometasone, fluticasone propionate or budesonide). The total incidence of perinatal abnormalities was higher in the group of asthmatic women not treated with ICS. However, this difference was non-significant ($p > 0.05$).

2.4.2 Controlled Clinical Trials

Recent results from the large-scale, international START study further support the safety of once-daily budesonide during pregnancy.[99] Among the 7241 patients who took part in the study, there were 319 pregnancies including 196 among women randomized to the budesonide (400 μg/day) arm of the study. The majority of pregnancies in both treatment arms resulted in the delivery of healthy babies (81% in the budesonide arm vs 77% in the placebo arm). There was no difference in the incidence of adverse outcomes between women randomized to budesonide and those who received placebo, including the incidence of spontaneous miscarriage, congenital abnormality or extrauterine pregnancy (figure 3).

2.4.3 Case Reports

Three reports of cases of congenital malformation in children born to asthmatic women treated with inhaled budesonide throughout their pregnancies were found in the literature. In one case, the woman was treated with multiple drugs, including intravenous and oral cortisone.[100] The child developed periventricular leukomalacia and retinopathy. In another case, the mother was treated for hyperthyroidism with the teratogenic drug thiamazole.[101] The child had multiple malformations including

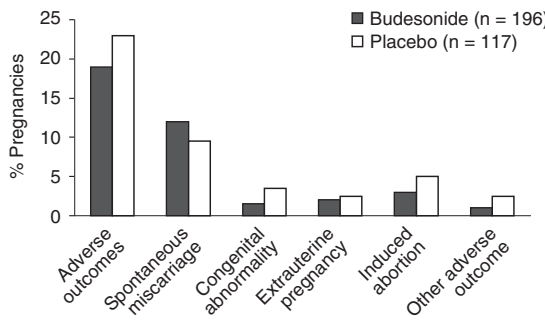

Fig. 3. Frequency of adverse outcomes of pregnancy among asthmatic women randomized to budesonide (400 μg/day) or placebo for up to 5 years.[99]

oesophagal atresia, choanalatresia and ventricular septal defects. In yet another case, a woman with achondroplasia delivered a child with trisomy 21 and achondroplasia.[102]

In one publication, a population-based cohort study in which paternal use of azathioprine or mercaptopurine before conception and the risk of congenital malformations is described.[103] One of the mothers who gave birth to a child with congenital malformations was given a prescription for budesonide during her pregnancy.

2.4.4 Summary of Data on Pregnancy

In summary, the literature indicates that adequate asthma control is of major importance for the pregnancy outcome regarding both mother and child. Large register studies and clinical trials indicate that inhaled budesonide does not increase the risk for the mother or child.

3. Discussion

Our review of the current evidence supports the long-term safety of budesonide therapy at recommended doses in terms of a number of key clinical safety endpoints, including adrenal crisis and insufficiency, final height, fracture risk and pregnancy outcomes.

Inhaled budesonide was first made available for the management of asthma in the early 1980s and has one of the longest safety records of the current commercially available ICS. Such an extensive evidence base is not yet available for other ICS and whether the apparent long-term safety of budesonide in key clinical areas can be extrapolated to other ICS is unclear; pharmacological and pharmacokinetic differences between the current ICS may contribute to differences in systemic exposure.[12,104,105] For example, the systemic half-life of budesonide is much shorter than that of fluticasone propionate as a result of its smaller volume of distribution. This can be partly explained by its low lipophilicity relative to fluticasone propionate and other ICS.[106] The reversible esterification process for budesonide occurs preferentially in the lung, and may serve as a local 'slow release' lung deposit of budesonide. This extends exposure at target and allows once-daily administration in milder forms of asthma. It also improves airway selectivity.[105,107] Efficiency of the delivery device to target the lungs may also influence systemic exposure by influencing the ratio of lung deposited drug to swallowed portion. In general, breath-activated dry-powder inhalators give a higher relative lung-deposition than pressurized metered dose inhalers.[108] Lung deposition of different ICS differs from a few percent to more than half the metered dose depending on device.[106]

Clinically relevant potential adverse effects of systemic exposure to corticosteroids, other than adrenal crisis, reduced final height, fractures and pregnancy outcome, were not addressed in the present review, largely because of the difficulty of defining clinical endpoints for cross-study evaluation. For example, systemic corticosteroid exposure has been associated with ophthalmological complications.[109] Although data have been published indicating little or no effect of even high doses of inhaled budesonide on intraocular pressure,[110] the relevant clinical endpoint – glaucoma – is more difficult to study. The risk of cataracts also presents a challenge in that a variety of definitions are used within the literature including lens opacities without impairment of vision rather than changes with impaired vision. At present, an observational 4-year cohort study[111] and randomized clinical trials[81,112] have not shown any increased risk of cataracts with budesonide in children.

3.1 Adrenal Crisis and Adrenal Insufficiency

From a review of the literature, it appears that acute adrenal crisis is an extremely rare complication of ICS therapy. The survey by Todd and colleagues[8] provides, to our judgement, the most reliable information about the problem because of three particular aspects. First, it was a nationwide (UK) survey. Second, certain criteria were set up for evaluating the specific diagnosis of adrenal crisis, and third, it was possible to compare patient exposure for different ICS based upon sales figures. According to this survey, there may be differences in the risk profiles of current ICS, with fluticasone pro-

pionate presenting the highest risk based on the clear predominance of adrenal crisis cases during fluticasone propionate therapy compared with other ICS. Although the majority of the patients had used fluticasone propionate at higher doses than licensed for the drug, many of them were not treated with higher doses than recommended in the British Guidelines on Asthma Management at the time.[113] Inhaled budesonide has been on the market since 1981 but the number of cases of adrenal crisis in patients receiving budesonide therapy is low and, for the cases with enough data presented to allow an analysis, explanations can be found for all cases except for one.[23] The most important explanations were combination with interacting medications that increase the systemic levels of budesonide (i.e. CYP3A4 inhibitors) in patients with cystic fibrosis, or too high a dose of corticosteroid either by combination with other corticosteroid treatment or treatment above the highest recommended dose for inhaled budesonide.

3.2 Final Height

Data on final height after long-term ICS treatment require long-term follow-up. An analysis after an average of 9.2 years' treatment showed that long-term treatment with budesonide had no significant effect on final adult height.[49] These findings are also supported by a later epidemiological study,[47] where ICS-treated children and adolescents were found to attain their final height at the same degree as healthy controls. However, assuming that adult height in ICS-treated asthmatic patients is reached at the same age as healthy individuals may underestimate the final adult height of the asthmatic patients[50] since 48.1% of the budesonide-treated patients achieved final height at age ≥20 years compared with only 11% of their 106 healthy siblings. It was concluded that adult height in children treated with inhaled budesonide is normal, but reached later than in healthy children. Because of the differences in the pharmacological properties, the reassuring data on final height generated for inhaled budesonide cannot necessarily be considered to be valid for other ICS.[14]

3.3 Fractures

Epidemiological studies provide contradictory results regarding increased risk of fractures associated with ICS; those epidemiological studies that suggest a potential increased risk of fractures mainly refer to ICS in general, rather than budesonide specifically, and the outcomes cannot automatically be extrapolated to budesonide because of differences in pharmacology and doses. In this review, all studies mentioning budesonide have been included, even if the number of patients treated with budesonide was small. Another problem with epidemiological studies is the ever-present risk of confounding factors, especially the underlying disease, and several studies have shown that COPD, asthma and allergic diseases all increase the fracture risk due to osteoporosis.[65,70,74,114-118]

Regarding fractures, epidemiological studies will mainly be hypothesis generating and any association with a particular substance and increased risk of fractures must be assessed by controlled clinical trials, preferably placebo-controlled and with focused investigations such as systematically performed relevant x-ray investigations. None of the budesonide-specific clinical trials (up to 800 μg/day) in this review demonstrate any increased risk of fractures. In addition, it should be noted that the search inclusion criteria exclude other clinical trials with budesonide where no fractures were reported.

3.4 Pregnancy

As expected, given the prevalence both of congenital malformations and of asthma, congenital malformations have been reported in children born to females who took ICS during pregnancy. However, upon more stringent examination of congenital malformations in children born to pregnant women taking inhaled budesonide using randomized, placebo-controlled clinical trials and epidemiological studies, no difference in incidence has been observed. Indeed, since 2000, the American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma and Immunology has recommended inhaled budesonide to pregnant asthmatic women.[119] Furthermore, on the basis of the

findings from the Swedish birth and health register,[87] US FDA re-categorized inhaled budesonide for use during pregnancy from Category C to Category B in 2001. Budesonide is the only ICS with a pregnancy Category B. These data were later confirmed in epidemiological studies[88,89] and the Asthma and Pregnancy Working Group of National Asthma Education and Prevention Program changed their recommendations in 2005 to include ICS, preferably inhaled budesonide, as first-line therapy for asthmatic pregnant women.[120,121] This reflects the expanding evidence-base supporting the safety of inhaled budesonide in pregnancy as well as the recognition that poorly controlled asthma is a significant health risk to both the mother and the fetus.

A recent study assessed budesonide concentrations in the milk and plasma of asthmatic nursing women receiving maintenance treatment with inhaled budesonide (200 μg or 400 μg twice daily).[122] Infant exposure was estimated based on average milk budesonide concentrations, and a single blood sample was obtained from five infants close to expected infant maximum concentration. Budesonide concentrations in infant plasma samples were all less than the limit of quantification, and the average plasma concentration in infants was estimated to be 1/600th of the concentrations observed in maternal plasma. Thus, there is a negligible systemic exposure to budesonide in breast-fed infants.[122]

4. Conclusion

Despite preclinical expectations, only long-term studies actually supply data on the safety of a product in the clinical setting. The official classification of inhaled budesonide for safe use in a sensitive patient population, such as pregnant women as discussed earlier, serves as a confirmation of the low risk of systemic adverse effects. Based on the evaluation of published literature on clinical safety endpoints, inhaled budesonide in recommended use only appears to be associated with the adverse effects associated with systemic corticosteroid exposure including adrenal crisis and insufficiency, final height, fracture risk and adverse pregnancy outcomes in very rare cases.

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References

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2006 [online]. Available from URL: http://www.ginasthma.org [Accessed 2007 Jan 17]
2. National Heart Lung and Blood Institute National Asthma Education Program Expert Panel report. Guidelines for the diagnosis and management of asthma. J Allergy Clin Immunol 1991; 88 (3 Pt 2): 425-534
3. International Asthma Management Project. International consensus report on diagnosis and management of asthma. Allergy 1992; 47 (13 Suppl.): 1-61
4. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999; 159 (9): 941-55
5. Pedersen S. Do inhaled corticosteroids inhibit growth in children? Am J Respir Crit Care Med 2001; 164 (4): 521-35
6. Price J, Hindmarsh P, Hughes S, et al. Evaluating the effects of asthma therapy on childhood growth: what can be learnt from the published literature? Eur Respir J 2002; 19 (6): 1179-93
7. Fuller R, Johnson M, Buye A. Fluticasone propionate: an update on preclinical and clinical experience. Respir Med 1995; 89 Suppl. A: 3-18
8. Todd GRG, Acerini CL, Ross-Russell R, et al. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002; 87 (6): 457-61
9. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006; 354 (19): 1985-97
10. Visser MJ, van der Veer E, Postma DS, et al. Side-effects of fluticasone in asthmatic children: no effects after dose reduction. Eur Respir J 2004; 24 (3): 420-5
11. Kelly HW. Potential adverse effects of the inhaled corticosteroids. J Allergy Clin Immunol 2003; 112 (3): 469-78
12. O'Connell EJ. Review of the unique properties of budesonide. Clin Ther 2003; 25 Suppl. C: C42-60
13. Thorsson L, Edsbäcker S, Källén A, et al. Pharmacokinetics and systemic activity of fluticasone via Diskus(R) and pMDI, and of budesonide via Turbuhaler. Br J Clin Pharmacol 2001; 52 (5): 529-38
14. Allen DB, Bielory L, Derendorf H, et al. Inhaled corticosteroids: past lessons and future issues. J Allergy Clin Immunol 2003; 112 (3 Suppl.): S1-S40
15. Molimard M, Pollet C, Girodet P, et al. Adrenal insufficiencies associated with inhaled corticosteroids: an under recognised event? [abstract no. 48]. Fundam Clin Pharmacol 2007; 21 Suppl. 1: 10

16. Daveluy A, Pollet C, Girodet P, et al. Adrenal insufficiency with inhaled corticosteroids: an under-recognised event? [abstract]. Drug Saf 2007; 30 (10): 24
17. Barton K. Fluticasone and adrenal suppression. Canadian Adverse Reaction Newsletter 2003; 13 (4): 2
18. Adverse Drug Reactions Advisory Committee (ADRAC). Fluticasone and adrenal crisis. Australian Adverse Drug Reactions Bulletin 2003; 22 (2): 6
19. Mjörndal T, Danell Boman M, Hagg S, et al. Adverse drug reactions as a cause for admissions to a department of internal medicine. Pharmacoepidemiol Drug Saf 2002; 11 (1): 65-72
20. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. Arch Dis Child 2002; 87 (6): 462-6
21. de Vries TW, de Langen-Wouterse JJ, van Puijenbroek E, et al. Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. Eur J Clin Pharmacol 2006; 62 (5): 343-6
22. Mortimer KJ, Tata LJ, Smith CJ, et al. Oral and inhaled corticosteroids and adrenal insufficiency: a case-control study. Thorax 2006; 61 (5): 405-8
23. Zwaan CM, Odink RJ, Delemarre-van de Waal HA, et al. Acute adrenal insufficiency after discontinuation of inhaled corticosteroid therapy. Lancet 1992; 340: 1289-90
24. Kajantie E, Otonkoski T, Kivirikko S, et al. A syndrome with multiple malformations, mental retardation, and ACTH deficiency. Am J Med Genet 2004; 126A (3): 313-8
25. Dunlop KA, Carson DJ, Shields MD. Hypoglycemia due to adrenal suppression secondary to high-dose nebulized corticosteroid. Pediatr Pulmonol 2002; 34 (1): 85-6
26. Wong J, Black P. Acute adrenal insufficiency associated with high dose inhaled steroids [letter]. BMJ 1992; 304 (6839): 1415
27. Main KM, Skov M, Sillesen IB, et al. Cushing's syndrome due to pharmacological interaction in a cystic fibrosis patient. Acta Paediatr 2002; 91 (9): 1008-11
28. Bolland MJ, Bagg W, Thomas MG, et al. Cushing's syndrome due to interaction between inhaled corticosteroids and itraconazole. Ann Pharmacother 2004; 38 (1): 46-9
29. Samaras K, Pett S, Gowers A, et al. Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. J Clin Endocrinol Metab 2005; 90 (7): 4394-8
30. Rask E, Eriksson JW, Forsberg G. Case reports of inhaled corticosteroid-induced adrenal suppression [in Swedish]. Läkartidningen 1997; 94 (40): 3529-30, 3533
31. Patel L, Wales JK, Kibirige MS, et al. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. Arch Dis Child 2001; 85 (4): 330-4
32. Todd GRG, Acerini CL, Buck JJ, et al. Acute adrenal crisis in asthmatics treated with high-dose fluticasone propionate. Eur Respir J 2002; 19 (6): 1207-9
33. Macdessi JS, Randell TL, Donaghue KC, et al. Adrenal crises in children treated with high-dose inhaled corticosteroids for asthma. Med J Aust 2003; 178 (5): 214-6
34. Todd GRG, Wright D, Ryan M. Acute adrenal insufficiency in a patient with asthma after changing from fluticasone propionate to budesonide. J Allergy Clin Immunol 1999; 103 (5): 956-7
35. De Swert LF, Wouters C, de Zegher F. Myopathy in children receiving high-dose inhaled fluticasone. N Engl J Med 2004; 350 (11): 1157-9
36. Baumgartner-Bonnevay C, Derharoutunian C, Daumont M, et al. Diabetes mellitus and adrenocortical insufficiency possibly associated with high-dose inhaled budesonide [in French]. Pharm Hosp 2000; 35 (143): 27-33
37. van Heest JA, Bokma JA, Van Oudheusden LJ, et al. Adrenocortical suppression attributed to budesonide [in Dutch]. Ned Tijdschr Geneeskd 1994; 138: 2204-7
38. De Wachter E, Vanbesien J, De Schutter I, et al. Rapidly developing Cushing syndrome in a 4-year-old patient during combined treatment with itraconazole and inhaled budesonide. Eur J Pediatr 2003; 162 (7-8): 488-9
39. De Wachter E, Malfroot A, De Schutter I, et al. Inhaled budesonide induced Cushing's syndrome in cystic fibrosis patients, due to drug inhibition of cytochrome P450. J Cyst Fibros 2003; 2 (2): 72-5
40. Jørgensen IM, Johansen HK, Frederiksen B, et al. Epidemic spread of Pandoraea apista, a new pathogen causing severe lung disease in cystic fibrosis patients. Pediatr Pulmonol 2003; 36 (5): 439-46
41. Zimmerman B, Gold M, Wherrett D, et al. Adrenal suppression in two patients with asthma treated with low doses of the inhaled steroid fluticasone propionate. J Allergy Clin Immunol 1998; 101 (3): 425-6
42. Bardelas JA, Krege JH. Case report: Addison's disease from inhaled fluticasone 880μg/day [abstract no. 728]. J Allergy Clin Immunol 2002; 109 (1 Suppl. S): S240
43. Todd G, Dunlop K, McNaboe J, et al. Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. Lancet 1996; 348 (9019): 27-9
44. Wilson AM, Blumsohn A, Jung RT, et al. Asthma and Cushing's syndrome. Chest 2000; 117 (2): 593-4
45. Molis WE, Hartz MF. Prolonged adrenal suppression during inhaled fluticasone and intranasal triamcinolone therapy [abstract no. P3]. Ann Allergy Asthma Immunol 2007; 98 (1 Suppl. 1): A35
46. Norjavaara E, Gerhardsson de Verdier M, Lindmark B. Reduced height in Swedish men with asthma at the age of conscription for military service. J Pediatr 2000; 137 (1): 25-9
47. Larsson L, Gerhardsson de Verdier M, Lindmark B, et al. Budesonide-treated asthmatic adolescents attain target height: a population-based follow-up study from Sweden. Pharmacoepidemiol Drug Saf 2002; 11 (8): 715-20
48. Van Bever HP, Desager KN, Lijssens N, et al. Does treatment of asthmatic children with inhaled corticosteroids affect their adult height? Pediatr Pulmonol 1999; 27 (6): 369-75
49. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000; 343 (15): 1064-9
50. Agertoft L, Pedersen S. Adult height in children treated with inhaled budesonide is normal but reached late [abstract no. P4080]. Eur Respir J 2006; 28 Suppl. 50: 709s
51. Agertoft L, Pedersen S. Adult height in children with asthma treated with inhaled budesonide is normal but reached at a later age than in healthy children [abstract]. Endocr Soc Annu Meet 2007; 457: P2-507
52. Adachi J. Corticosteroid-induced osteoporosis. Int J Fertil Womens Med 2001; 46 (4): 190-205
53. Lalloo UG, Malolepszy J, Kozma D, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. Chest 2003; 123 (5): 1480-7

54. Leflein JG, Baker JW, Eigen H, et al. Safety features of budesonide inhalation suspension in the long-term treatment of asthma in young children. Adv Ther 2005; 22 (3): 198-207
55. Pohunek P, Kuna P, Jorup C, et al. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatr Allergy Immunol 2006; 17 (6): 458-65
56. Möller C, Strömberg L, Oldaeus G, et al. Efficacy of once-daily versus twice-daily administration of budesonide by Turbuhaler in children with stable asthma. Pediatr Pulmonol 1999; 28 (5): 337-43
57. Bisgaard H, Le Roux P, Bjamer D, et al. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. Chest 2006; 130 (6): 1733-43
58. Davis KJ, Clark D, Knobil K. Inhaled corticosteroid use and risk of non-vertebral fracture among adults with chronic obstructive lung disease in UK general practice [abstract]. Chest 2003; 124 (4 Suppl. S): 166S
59. van Staa TP, Leufkens HGM, Cooper C. Use of inhaled corticosteroids and risk of fractures. J Bone Miner Res 2001; 16 (3): 581-8
60. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with systemic and topical corticosteroids. J Intern Med 2005; 257 (4): 374-84
61. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in patients with chronic lung diseases treated with bronchodilator drugs and inhaled and oral corticosteroids. Chest 2007; 132 (5): 1599-607
62. Hubbard RB, Smith CJP, Smeeth L, et al. Inhaled corticosteroids and hip fracture: a population-based case-control study. Am J Respir Crit Care Med 2002; 166 (12): 1563-6
63. Vestergaard P, Olsen ML, Johnsen SP, et al. Corticosteroid use and risk of hip fracture: a population-based case-control study in Denmark. J Intern Med 2003; 254 (5): 486-93
64. de Vries F, Pouwels S, Lammers JWJ, et al. Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study. J Intern Med 2007; 261 (2): 170-7
65. de Vries F, van Staa TP, Bracke M, et al. Severity of obstructive airway disease and risk of osteoporotic fracture. Eur Respir J 2005; 25 (5): 879-84
66. Schlienger RG, Jick SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics 2004; 114 (2): 469-73
67. Johannes CB, Schneider GA, Dube TJ, et al. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest 2005; 127 (1): 89-97
68. Pujades-Rodríguez M, Smith CJP, Hubbard RB. Inhaled corticosteroids and the risk of fracture in chronic obstructive pulmonary disease. Q J Med 2007; 100 (8): 509-17
69. Suissa S, Baltzan M, Kremer R, et al. Inhaled and nasal corticosteroid use and the risk of fracture. Am J Respir Crit Care Med 2004; 169 (1): 83-8
70. van Staa TP, Bishop N, Leufkens HGM, et al. Are inhaled corticosteroids associated with an increased risk of fracture in children? Osteoporos Int 2004; 15 (10): 785-91
71. Hubbard R, Tattersfield A, Smith C, et al. Use of inhaled corticosteroids and the risk of fracture. Chest 2006; 130 (4): 1082-8
72. Lau E, Mamdani M, Tu K. Inhaled or systemic corticosteroids and the risk of hospitalization for hip fracture among elderly women. Am J Med 2003; 114 (2): 142-5
73. Walsh LJ, Lewis SA, Wong CA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. Am J Respir Crit Care Med 2002; 166 (5): 691-5
74. Ferencz V, Meszaros S, Csupor E, et al. Increased bone fracture prevalence in postmenopausal women suffering from pollen-allergy. Osteoporos Int 2006; 17 (3): 484-91
75. Tattersfield AE, Town GI, Johnell O, et al. Bone mineral density in subjects with mild asthma randomised to treatment with inhaled corticosteroids or non-corticosteroid treatment for two years. Thorax 2001; 56 (4): 272-8
76. Johnell O, Pauwels R, Lofdahl CG, et al. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler®. Eur Respir J 2002; 19 (6): 1058-63
77. Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999; 340 (25): 1948-53
78. Pedersen S, O'Byrne PM, Busse WW, et al. Fracture rate in patients with asthma receiving long-term early intervention with budesonide: the START study [abstract no. P1855]. Eur Respir J 2005; 26 Suppl. 49: 276s
79. Sheffer AL, Silverman M, Woolcock AJ, et al. Long-term safety of once-daily budesonide in patients with early-onset mild persistent asthma: results of the Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study. Ann Allergy Asthma Immunol 2005; 94 (1): 48-54
80. Silverman M, Sheffer AL, Diaz PV, et al. Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial. Pediatr Allergy Immunol 2006; 17 Suppl. 17: 14-20
81. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med 2000; 343 (15): 1054-63
82. Murphy VE, Gibson P, Talbot PL, et al. Severe asthma exacerbations during pregnancy. Obstet Gynecol 2005; 106 (5 Pt 1): 1046-54
83. Otsuka H, Narushima M, Suzuki H. Assessment of inhaled corticosteroid therapy for asthma treatment during pregnancy. Allergol Int 2005; 54 (3): 381-6
84. Wen SW, Demissie K, Liu S. Adverse outcomes in pregnancies of asthmatic women: results from a Canadian population. Ann Epidemiol 2001; 11 (1): 7-12
85. Sorensen TK, Dempsey JC, Xiao R, et al. Maternal asthma and risk of preterm delivery. Ann Epidemiol 2003; 13 (4): 267-72
86. Kelly YJ, Brabin BJ, Milligan P, et al. Maternal asthma, premature birth, and the risk of respiratory morbidity in schoolchildren in Merseyside. Thorax 1995; 50 (5): 525-30
87. Källén B, Rydhstroem H, Åberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999; 93 (3): 392-5
88. Källén BAJ, Otterblad Olausson P. Maternal drug use in early pregnancy and infant cardiovascular defect. Reprod Toxicol 2003; 17 (3): 255-61
89. Norjavaara E, Gerhardsson de Verdier M. Normal pregnancy outcomes in a population-based study including 2968 pregnant women exposed to budesonide. J Allergy Clin Immunol 2003; 111 (4): 736-42
90. Källén B, Otterblad Olausson P. Use of anti-asthmatic drugs during pregnancy: 3. Congenital malformations in the infants. Eur J Clin Pharmacol 2007; 63 (4): 383-8

91. Blais L, Beauchesne M-F, Rey E, et al. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. Thorax 2007; 62 (4): 320-8

92. Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007; 197 (6): 585.e1-7

93. Tamasi L, Somoskovi A, Muller V, et al. A population-based case-control study on the effect of bronchial asthma during pregnancy for congenital abnormalities of the offspring. J Asthma 2006; 43 (1): 81-6

94. Namazy J, Schatz M, Long L, et al. Use of inhaled steroids by pregnant asthmatic women does not reduce intrauterine growth. J Allergy Clin Immunol 2004; 113 (3): 427-32

95. Bakhireva LN, Jones KL, Schatz M, et al. Asthma medication use in pregnancy and fetal growth. J Allergy Clin Immunol 2005; 116 (3): 503-9

96. Murphy VE, Gibson PG, Giles WB, et al. Maternal asthma is associated with reduced female fetal growth. Am J Respir Crit Care Med 2003; 168 (11): 1317-23

97. Murphy VE, Smith R, Giles WB, et al. Reduced 11beta-hydroxysteroid dehydrogenase type 2 activity is associated with decreased birth weight centile in pregnancies complicated by asthma. J Clin Endocrinol Metab 2002; 87 (4): 1660-8

98. Clifton VL, Rennie N, Murphy VE. Effect of inhaled glucocorticoid treatment on placental 11beta-hydroxysteroid dehydrogenase type 2 activity and neonatal birthweight in pregnancies complicated by asthma. Aust N Z J Obstet Gynaecol 2006; 46 (2): 136-40

99. Silverman M, Sheffer A, Diaz PV, et al. Outcome of pregnancy in a randomized controlled study of patients with asthma exposed to budesonide. Ann Allergy Asthma Immunol 2005; 95 (6): 566-70

100. Hagwall N, Engström E, Hellström A, et al. Periventricular leukomalacia and retinopathy in a term infant born to a mother with asthma. Dev Med Child Neurol 2006; 48 (4): 301-3

101. Johnsson E, Larsson G, Ljunggren M. Severe malformations in infant born to hyperthyroid woman on methimazole [letter]. Lancet 1997; 350 (9090): 1520

102. DeRenzo JS, Vallejo MC, Ramanathan S. Failed regional anesthesia with reduced spinal bupivacaine dosage in a parturient with achondroplasia presenting for urgent cesarean section. Int J Obstet Anesth 2005; 14 (2): 175-8

103. Nørgård B, Pedersen L, Jacobsen J, et al. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. Aliment Pharmacol Ther 2004; 19 (6): 679-85

104. Allen DB. Influence of inhaled corticosteroids on growth: a pediatric endocrinologist's perspective. Acta Paediatr 1998; (2): 123-9

105. Derendorf H. Corticosteroid pharmacokinetic/pharmacodynamic parameters and their relationship to safety and efficacy. Allergy Asthma Proc 2005; 26 (5): 327-35

106. Edsbäcker S, Johansson CJ. Airway selectivity: an update of pharmacokinetic factors affecting local and systemic disposition of inhaled steroids. Basic Clin Pharmacol Toxicol 2006; 98 (6): 523-36

107. Brattsand R, Miller-Larsson A. The role of intracellular esterification in budesonide once-daily dosing and airway selectivity. Clin Ther 2003; 25 Suppl. 3: C28-41

108. Borgström L, Bengtsson T, Derom E, et al. Variability in lung deposition of inhaled drug, within and between asthmatic patients, with a pMDI and a dry powder inhaler, Turbuhaler®. Int J Pharm 2000; 193 (2): 227-30

109. Aronson J. Corticosteroids: glucocorticoids. In: Meyler's side effect of drugs: the international encyclopedia of adverse drug reactions and interactions. 15th ed. Oxford: Elsevier, 2006: 906-58

110. Duh MS, Walker AM, Lindmark B, et al. Association between intraocular pressure and budesonide inhalation therapy in asthmatic patients. Ann Allergy Asthma Immunol 2000; 85 (5): 356-61

111. Agertoft L, Larsen FE, Pedersen S. Posterior subcapsular cataracts, bruises and hoarseness in children with asthma receiving long-term treatment with inhaled budesonide. Eur Respir J 1998; 12 (1): 130-5

112. Turpeinen M, Kari O, HEICA study group. Posterior subcapsular opacities not observed in children treated for 18 months with budesonide Turbuhaler® [abstract no. P1936]. Eur Respir J 2001; 18 Suppl. 33: 290s

113. British Thoracic Society. The British guidelines on asthma management: 1995 review and position statement. Thorax 1997; 52 Suppl. 1: S1-20

114. de Vries F, Pouwels S, Bracke M, et al. Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study. Pharmacoepidemiol Drug Saf 2006; 16 (6): 612-9

115. Soriano JB, Visick GT, Muellerova H, et al. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005; 128 (4): 2099-107

116. Jørgensen NR, Schwarz P, Holme I, et al. The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross sectional study. Respir Med 2007; 101 (1): 177-85

117. Bolton CE, Ionescu AA, Shiels KM, et al. Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004; 170 (12): 1286-93

118. Sabit R, Bolton CE, Edwards PH, et al. Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; 175 (12): 1259-65

119. Callaghan ML. Position statement: the use of newer asthma and allergy medications during pregnancy. Ann Allergy Asthma Immunol 2000; 84 (5): 475-80

120. NAEPP Expert Panel Report. Managing asthma during pregnancy: recommendations for pharmacologic treatment. 2004 update. J Allergy Clin Immunol 2005; 115 (1): 34-46

121. Gluck PA, Gluck JC. A review of pregnancy outcomes after exposure to orally inhaled or intranasal budesonide. Curr Med Res Opin 2005; 21 (7): 1075-84

122. Fält A, Bengtsson T, Kennedy B-M, et al. Exposure of infants to budesonide through breast milk of asthmatic mothers. J Allergy Clin Immunol 2007; 120 (4): 798-802

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