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Position paper

Inhaled and nasal corticosteroids: safety aspects*

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Introduction

The commercially available inhaled corticosteroids (ICS) for asthma treatment are beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate (FP), mometasone furoate (MF), and triamcinolone acetonide (TA); most of them are also available as nasal sprays for the treatment of rhinitis. There is no longer any doubt of their effectiveness in both asthma and rhinitis. Since ICS are widely used in both adults and children, the issue of safety and the risk/benefit ratio assume primary importance. The present position paper focuses on the clinical and biological aspects of the safety of ICS; therefore, the available literature is reviewed in order to reach experimentally supported conclusions useful for

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This document represents the "state of the art", and is based on the literature available as of December 1998. The efficacy and safety of inhaled and nasal corticosteroids is a fast-changing field; therefore, this position paper will be updated as frequently as required by new experimental evidence.

both specialists and general practitioners. Since this position paper specifically addresses the subject of safety, other important aspects (e.g., clinical efficacy, mode of administration, pharmacokinetic-pharmacodynamic properties, etc.) are not discussed, although relevant reviews are cited.

Asthma is defined clinically by reversible airways obstruction and bronchial hyperresponsiveness, and, pathologically, by chronic bronchial inflammation involving various cells and mediators (1). The symptomatic relief of bronchospasm is no longer the only therapeutic target. Control of the inflammatory component of asthma is equally important, especially for long-term management of the disease. At present, ICS are the most effective drugs for reducing bronchial inflammation. Their primary therapeutic role is widely accepted for all types of asthma (1–4). ICS reduce the inflammatory infiltrate in the bronchi (5–11) and, at least in part, reverse the anatomical alterations in the bronchial wall usually detected in asthma (12, 13). Although ICS are highly effective in controlling symptoms and bronchial inflammation, clinical relapse and the reappearance of bronchial inflammation are usually observed after their discontinuation (14–17). Therefore, long-term treatment for effective asthma control is usually required.

The mechanism of action of glucocorticoids involves binding to a specific intracytoplasmic receptor that subsequently migrates into the nucleus and modulates the transcription of specific target genes. These genes encode for cytokines, lipocortin-1, endothelin, β-adrenoceptors, iNOS, endopeptidases, etc. Several transcription factors are involved in this mechanism (18–24). ICS exert their clinical and anti-inflammatory actions directly on the bronchial wall; therefore, these effects depend upon a wide range of variables, including the status of the bronchial wall (12, 13, 25), the pharmacodynamic-pharmacokinetic properties of the drug (26–30), the delivery system (31–34), the patient's cooperation (35–38), and the dosage regimen (39–41). These factors also determine the severity and frequency of side-effects.

Systemic side-effects

The more relevant systemic side-effects of ICS concern adrenal gland function, bone metabolism, and growth pattern in children/adolescents. Due to the widespread use of ICS, these side-effects have been extensively investigated in several controlled studies by means of biochemical, metabolic, and morphofunctional parameters. The occurrence and severity of these side-effects depend, as mentioned above, upon a large number of variables, including the characteristics of the drug (lipophilicity, pharmacokinetics, and pharmacodynamics) and the mode of administration (dose, delivery system, coordination, etc.). Therefore, it is often difficult to reach an unequivocal conclusion; nevertheless, based on consistent experimental evidence, some useful suggestions can be provided (42).

Hypothalamic-pituitary-adrenal axis (HPAA)

Long-term treatment with oral corticosteroids may result in significant suppression of the HPAA: exogenous steroids, through negative feedback, suppress corticotrophin secretion, thus leading to adrenal cortex atrophy and to subsequent decrease of cortisol secretion (43). This effect is pronounced and long-lasting with oral corticosteroids. ICS may also have some measurable effect on the HPAA (44). Since ICS are used for long-term treatment, assessment of their effects on the HPAA is of primary relevance from the viewpoint of safety.

There are several standardized methods for assessing the integrity of the HPAA both in static and dynamic conditions. They include morning cortisol, ACTH levels, integrated (AUC) cortisol levels overnight, free urinary cortisol level over 24 h (usually with creatinine correction), ACTH (tetracosactrin) stimulation, the metyrapone test, and insulin-induced hypoglycaemia (45–47). A single morning cortisol level is weakly sensitive due to wide variations of this variable in the same subject. The integrated overnight cortisol measurement can detect also the disappearance of physiological peaks of secretion; therefore, it is a reliable test, although it requires multiple blood sampling. The free urinary cortisol over 24 h appears to be a practical and reliable index, since it provides a global evaluation of the adrenal function, and it is not influenced by circadian changes in cortisol blood levels (45–51); however, obtaining a complete 24-h urine sample may be problematic. The dynamic tests assess the integrity of the whole HPAA, but they can be performed only in selected centres and they often cause discomfort to patients; therefore, they are not commonly used for clinical trials.

Some studies have been performed in healthy subjects. In one, it was shown that BDP exerted a greater (approximately twofold) suppressive effect on the HPAA than BUD, in a single dose (200, 800, or 3200 μg) (52). In another one, BUD 400 μg single dose, or 400 μg b.i.d. for 2 weeks, significantly suppressed the adrenal function (53). Two dose-response studies (54, 55) showed that FP (up to 2000 μg/day) is more potent in reducing the daily plasma cortisol level (dose-dependent) than BUD (up to 1600 μg/day), although it is difficult to compare the dosage of two different molecules. Grove et al. (56) found a significant effect on the ACTH test by FP (750–1500 μg) and BUD (800–1600 μg) with no difference between the drugs. Wilson et al. showed that both FP (average 1625 μg/day) and TA (1600 μg/

day) suppressed the urinary cortisol excretion, but only FP affected plasma cortisol levels (57). On the other hand, studies by Braun et al. (58) found that BDP and BUD at high dosages (>2000 μg) did not significantly affect urinary free cortisol levels, if administered by a large-volume spacer.

When administered at high dosages (>1200 μg in adults or >800 μg in children), BDP exerted a significantly more prominent effect on the HPAA than BUD, and this effect was dose-related (59–62). Nevertheless, the inhibitory action on the HPAA by BDP and BUD was found to be, respectively, eight- and fivefold lower than that by systemic prednisone (63). In two studies (64, 65) assessing the integrated cortisol level in children, BDP 1000 μg affected the physiological rhythm of cortisol secretion. In another study in children, BUD (200, 400, and 800 μg/day) did not affect the urinary cortisol (66). In a long-term study (1 year) on moderate to severe asthma, FP (1500 μg/day) was demonstrated to be more effective than BDP and devoid of effects on the HPAA (67). Langdon & Capsey (68) reported that FP (400 μg/day) given as a dry powder was as effective as BUD (800 μg/day) and did not affect the morning blood cortisol level of adult asthmatics. On the contrary, in another study, FP (2000 μg/day) exerted a significantly more pronounced inhibitory effect on the HPAA than BDP (1600 μg/day) in adults (69). In a single-dose, dose-response comparative study by Clark et al., FP (2000 μg) was shown to be threefold more potent than BUD (2000 μg) in reducing the overnight urinary cortisol excretion (70); a superimposable result was obtained in children with FP and BUD up to 1250 μg/day (71) and in adults on chronic treatment (72). In a long-term study in asthmatic children (up to 5 years), Volovitz et al. (73) demonstrated that BUD (200 μg/day) did not significantly influence HPAA function. The administration of 400 μg/day of BUD or BDP for 2 weeks in asthmatic children resulted in a reduction of free urinary cortisol, without differences between the two compounds (74). Similar results (75) were obtained with the same drugs at higher doses (>400 μg/day). Interestingly, a controlled study on asthmatic children receiving 250–1000 μg/day BDP showed that a significant reduction of 24-h urinary cortisol occurred in patients using a metered-dose inhaler (MDI), but not in those using a spacer device (76). Similar results were obtained in children receiving BUD (100 μg b.i.d.) or FP (200 μg b.i.d.) through a spacer, in whom no adrenal suppression was seen (77); the same effect was also observed with BUD up to 400 μg/day administered through a spacer device (78), whereas FP 200–400 μg/day and BUD 400 μg/day by Turbohaler/Diskhaler reduced the urinary free cortisol excretion (79). No significant effect on the HPAA was observed with FP (100–200 μg/day) (80) in a long-term study performed on asthmatic children. High doses of FLU and TA (>1000 μg/day) appeared to have no effect on free urinary cortisol (81, 82). FP and BUD 400 μg/day for 4 weeks did not affect the plasma cortisol levels in asthmatic children, although FP showed a slightly more pronounced effect (83). A recent meta-analysis study conducted on FP, BUD, and BDP showed that FP and BDP did not affect plasma cortisol levels, while a significant reduction was observed with BUD (84). Finally, some clinical trials have confirmed the safety of ICS-only treatment in children (85, 86), and a recovery of adrenal function after oral steroid reduction and introduction of ICS (87–89). The results are summarized in Table 1.

Most available papers refer to BUD, BDP, and FP. These drugs can influence the HPAA in a dose-dependent manner (the effect can often be detected even after a single dose). This effect seems to occur when doses of >800 μg/day in adults and >400 μg/day in children are used (90). Finally, acute adrenal failure consequent on ICS withdrawal (91, 92) or Cushing's syndrome (93, 94) has been reported only anecdotally.

In conclusion, the effects of ICS on the HPAA can be detected only by using sensitive biochemical methods; therefore, it is difficult to demonstrate their clinical counterpart and their clinical significance: in none of the controlled studies were signs or symptoms of adrenal failure described.

Bone metabolism (Table 2)

Oral corticosteroids may induce osteoporosis and increase the risk of fractures in adult patients (95–97). The effects of corticosteroids on bone metabolism mainly involve the trabecular structure and are mediated by a number of mechanisms at different sites of action (96). Firstly, corticosteroids reduce intestinal calcium absorption and enhance its renal excretion; these actions result in compensatory secretion of parathormone, bone resorption, and increased activity of osteoclasts. Secondly, corticosteroids inhibit osteoblastic activity and the synthesis of osteocalcin. Thirdly, steroids reduce the synthesis of adrenal cortex-derived oestrogens. This last finding partly explains the increased risk of osteoporosis in postmenopausal women (98, 99). Once again, since ICS are frequently used at high doses and for long-term treatment, a careful evaluation of their effects on bone is required (99, 100).

These effects are commonly assessed by biochemical methods (Table 3), which evaluate calcium metabolism (calcium, phosphate, and parathyroid hormone) and the enzymatic activities involved in bone turnover and some products of bone catabolism. They include serum osteocalcin, alkaline phosphatase, procollagen I carboxyterminal propeptide (PICP), procollagen III N-terminal propeptide (PIIINP) (as indices of bone synthesis), urinary hydroxyproline, urinary calcium, serum pyridine cross-links, and type I collagen carboxyterminal

Table 1. Effects on HPAA in asthmatics

Author, year	Ref.	A/C *	Drug Dose μg/day	Duration	Test	Result
Sly, 1978	81	C	TA 100	2 months	Basal cortisol	No effect
Law, 1986	64	C	BDP 100	2 weeks	Cortisol AUC	↓ AUC
Ebden, 1986	60	A	BUD 1600 BDP 1500	6 weeks	Basal cortisol ACTH test	↓ Cortisol; no effect on ACTH test for both drugs
Prahl, 1987	86	C	BDP (mean 1965)	>2 weeks	Basal cortisol, ACTH test Free urinary cortisol	Suppression only with BDP >2500 μg/day
Pedersen, 1988	62	C	BUD 800–1200 BDP 800–1000	6 weeks	Free urinary cortisol	↓ Urinary cortisol BDP no effect BUD
Bisgaard, 1988	59	C	BUD 200, 400, 800 BDP 200, 400, 800	4 weeks dose	Free urinary cortisol ACTH test	Dose-dependent suppression More pronounced for BDP No effect on ACTH test
Varsano, 1990	85	C	BUD 200	1 year	Basal cortisol, ACTH test	No effect
Piacentini, 1990	82	C	FLU 1000	2 months	Basal cortisol, ACTH test Free urinary cortisol	No effect
Bisgaard, 1991	66	C	BUD 200, 400, 800	8 weeks/ dose	Free urinary cortisol	No effect at each dose
Svendsen, 1992	61	A	BUD 800 BDP 750	6 weeks	Basal cortisol	No effect
Phillip, 1992	65	C	BDP 200–450	>6 months	Cortisol AUC ACTH test	↓ Dose independent No effect on ACTH test
Fabbri, 1993	67	A	FP/BUD 1500	2 weeks	Free urinary cortisol	No effect
Ninan, 1993	75	C	BUD/BDP 400	2 weeks	Basal cortisol, ACTH test	↓ Cortisol, ↓ ACTH for both drugs
Hoffman, 1993	80	C	FP 100–200 BUD 800	2 weeks	Basal cortisol	No effect
Volovitz, 1993	73	C	BUD 200	3–5 years	Basal cortisol ACTH test	No effect
Nikolaizik, 1994 both drugs	74	C	BUD/BDP 400	4 weeks	Free urinary cortisol, ACTH test, GH	↓ HPAA with both drugs No effect on GH and ACTH
Langdon, 1994	68	A	FP 400 BUD 800	2 weeks	Basal cortisol	No effect
Boe, 1994	69	A	FP 2000 BUD 1600	4 weeks	Free urinary cortisol	↓ FP No effect BUD
Pedersen, 1995	78	C	BUD 100, 200, 400	4 weeks/ dose	Free urinary cortisol	No effect
Clark, 1996	70	A	FP 1000, 1500, 2000 BUD 1000, 1600, 2000	Single dose	Plasma cortisol	↓ FP 1500 and 2000 ↓ BUD 2000
Clark, 1996	71	C	FP or BUD 400, 800, 1250 (spacer)	Single dose	Free urinary cortisol	↓ For FP each dose No effect BUD
Hoekx, 1996	83	C	BUD/FP 400	4 weeks	Plasma cortisol	No effect
Goldberg, 1996	76	C	BDP 200–1000 With/without spacer	>4 months	Free urinary cortisol	↓ Only without spacer
Agertoft, 1997	79	C	FP 200–400 BUD 200–400	2 weeks/ dose	Free urinary cortisol	↓ With FP both doses and BUD 400
Lipworth, 1997	77	C	FP 200 (spacer) BUD 400 (spacer)	2 weeks	Free urinary cortisol	No effect
Clark, 1997	72	A	BUD or FP 500, 1000, 2000	2 weeks	Free urinary cortisol Plasma cortisol	↓ Significant for FP

* Adult/child. GH: growth hormone.

telopeptide (ICTP) (as indices of bone resorption) (101–104). Bone density can also be assessed by dual X-ray absorptiometry (DEXA) or ultrasound densitometry of skeletal segments (105); generally, the lumbar spine and the neck of the femur are studied.

Also in this case, the majority of data are available for BDP, BUD, and FP; therefore, no conclusive statement can be given on the other compounds. In general, experimental evidence does not support an increased risk of osteoporosis or pathologic fractures in either adults or children (106–108). Short-term studies, all performed with moderate to high doses of BUD or BDP, showed a decrease in serum osteocalcin and increased urinary hydroxyproline; these effects were strictly dose-related (109–111). High doses of BUD (1600 μg/day) when administered through spacers to premenopausal women did not influence osteocalcin, while BDP (2000 μg/day) did so (112). The reduction of serum osteocalcin exerted by BDP (500 μg b.i.d.) was less marked than with prednisolone (15 mg/day) in a

Table 2. Studies on effects of ICS on bone metabolism

Author, year	Ref.	A/C *	Drug Dose μg/day	Duration	Test	Result
Teeluksingh, 1991	108	A	BDP 400–2000	4 weeks	Osteocalcin	↓ Dose dependent
Pouw, 1991	109	A	BDP 2000	1 week	Osteocalcin	↓ Dose dependent
Ali, 1991	110	A	BUD 1800 BDP 2000	4 weeks	Urinary hydroxyproline ALP, PTH	↑ Hydroxyproline with BDP No effect BUD
Packe, 1992	106	A	BDP 800–2000 plus oral steroids	3 weeks	Bone mass density	↓ Dose dependent and with oral steroids
Sorva, 1992	111	C	BUD 400–800	3 months	PICP, ALP, osteocalcin	↓ All doses
Leech, 1993	112	A	BUD 1600/800 BDP 2000/1000	1 wk	Osteocalcin	↓ BDP, BUD no effect, ½ dose no effect
Konig, 1993	117	C	BDP 300–800	>6 months	Ostocalcin, bone mass density	No effect
Wolthers, 1993	118	C	BUD 800	4 weeks	Osteocalcin	No effect
Ip, 1994	107	A	Various, 400–2000	>1 month	Bone mass density	↓ Dose dependent
Baraldi, 1994	119	C	BDP 400-800	1 month	Osteocalcin	↓
Kinberg, 1994	120	C	BDP 400	Various	Bone mass density	No effect
Boulet, 1994	124	A	BDP/BUD >800	>18 months	Urinary phosphate, bone mass, osteocalcin	↑ Urinary phosphate =bone mass and osteocalcin
Kerstjens, 1994	125	A	BUD/BDP 800	2.5 years	PICP, ICTP	No effect
Meeran, 1995	113	A	BDP 1000	1 week	Osteocalcin	No effect
Meeran, 1995	114	A	BDP 500 with and without spacer	1 week	Osteocalcin	↓ Only without spacer
Toogood, 1995	115	A	BUD 1500 BDP 1500 (plus oral)	5–10 years	Bone mass density	↓ Only at highest doses
Birkebaek, 1995	126	C	BUD/BDP 800	2 weeks	PICP, PIIINP, osteocalcin	↓ PICP, PIIINP, unchanged osteocalcin
Wolthers, 1995	127	C	BUD 200, 400, 800	2 weeks/ dose	ICTP, PIIINP	↓ Only at 800
Hopp, 1995	122	C	BDP 200–450	>4 months	Bone mass density	No effect
Hoekx, 1996	83	C	BUD/FP 400	4 weeks	PICP, ICTP	No effect
Martinati, 1996	123	C	BDP 400	>4 months	Bone mass density	No effect
Bootsma, 1996	128	A	FP 750 BDP 1500	6 weeks	Osteocalcin, ICTP	↓ BDP No effect FP
Agertoft, 1997	79	C	FP 200–400 BUD 200–400	2 weeks/ dose	Knemometry	↓ With FP and BUD 400; no effect 200
Agertoft, 1998	121	C	BUD 200–1300	3–6 years	Bone mass density	No effect
Martinati, 1998	129	C	BDP 150–400	7 months	Bone mass density	No effect

* Adult/child.

7-day course of therapy (113), and it could be minimized by using a large-volume spacer (114). Toogood et al. (115) demonstrated that long-term treatment with BDP or BUD (1000 μg/day or more) did not significantly affect either bone density or the risk of bone fracture if administered through spacers. Neither FP (1000–2000 μg/day) nor BUD (1600 μg/day) significantly reduced serum osteocalcin (116). In children, BUD (800 μg/day) and BDP (800 μg/day) did not alter any biochemical marker of bone metabolism (117, 118). BDP (300–400 μg/day) in asthmatic compared to normal children did not have any detectable effect on

Table 3. Methods used to investigate bone metabolism

Calcium metabolism	Bone formation	Bone resorption	Bone density
Plasma calcium levels	Osteocalcin	Glycosylated hydroxylysine	Dual X-ray absorptiometry (DEXA)
Plasma phosphate levels	Alkaline phosphatase (ALP)	Pyridinoline/ deoxypyridinoline	Ultrasound densitometry
Parathyroid hormone (PTH)	Procollagen I carboxy terminal propeptide (PICP)	Tartrate-resistant alkaline phosphatase (TRAP)	
Urinary calcium/phosphate	Procollagen I N-terminal propeptide (PINP)	Hydroxyproline	
	Procollagen III N-terminal propeptide (PIIINP)	Cross-linked carboxy terminal telopeptide of type 1 collagen (ICTP)	

bone density (119). These results were confirmed in several other controlled studies with BUD and BDP in asthmatic children (120–122). Similarly, in a long-term treatment with BDP (200–400 μg/day), no significant detectable effect on bone mass was observed in adolescents (123). Although an increase in urinary phosphate and a reduction in serum osteocalcin concentrations were observed, no change in bone density was detectable in adult patients taking ICS at high dosages (BUD or BDP >800 μg/day) for up to 18 months (124). No changes in serum procollagen type I telopeptide were observed in patients receiving BUD or BDP (800 μg/day) for more than 2 years (125). On the other hand, a slight reduction in collagen types I and III turnover was seen with BUD and BDP 800 μg/day (126), while BUD 400 μg/day only reduced the turnover of type III collagen (127). Bootsma et al. (128) compared the effects of FP (750 μg/day) and BDP (1500 μg/day) in asthmatics after short courses of treatment; they found that BDP, but not FP, affected the serum osteocalcin levels. In asthmatic children, FP and BUD 400 μg/day did not affect the markers of bone resorption and formation (83). Finally, Martinati et al. (129) found no change in the bone mass density, measured through absorptiometry, of asthmatic children treated for 4 months or more with BDP (150–400 μg/day).

Although certain effects of ICS on bone metabolism are detectable, they are evident only by laboratory assessment, when high doses are used. In particular, in none of the studies assessing bone mass density was a significant effect found (Table 2). Moreover, in several studies, the confounding effects of short courses of oral steroids have also to be taken into account. The clinical relevance of the effects on bone metabolism is questionable, since an increased risk of fractures or osteoporosis has never been substantiated. However, in view of the documented bioavailability of high-dose ICS and possible effects on the HPAA, it is advisable to use the lowest effective doses to maintain asthma control.

Growth in childhood (Table 4)

Since ICS are widely prescribed in paediatric patients, often for long-term treatment, their possible effects on growth pattern have been carefully investigated. Untreated asthma itself significantly affects the growth and final stature of children, as was clearly documented as early as 1868 (130). This was subsequently confirmed in prospective studies, which showed that asthma may reduce the growth pattern of children and may reduce their potential height or, at least, the growth velocity (131–134). The growth deceleration seems to correlate well with the pulmonary function impairment (134).

Table 4. ICS and growth in children and adolescents

Author, year	Ref.	Drug Dose μg/day	Assessment	Duration	Result
Balfour-Lynn, 1986	136	BDP 400–600	Final height	13 years	No effect on height Retardation of puberty
Varsano, 1990	85	BUD 200	Height and weight	1 year	No effect
Wolthers, 1991	147	BUD 200, 400, 800	Knemometry	18 days dose	Dose dependent ↓ of growth velocity
Ninan, 1992	140	BDP various doses	Growth velocity	>1 year	Direct correlation with asthma control. No effect of ICS
Wolthers, 1992	148	BUD 200, 400, 800	Knemometry	2 months	↓ With BUD 800 No effect with 200–400
Wolthers, 1993	149	FP 200 BDP 400, 800	Knemometry	2 weeks	↓ With BDP 400/800 No effect with FP 200
Volovitz, 1993	73	BUD 200	Height, weight Growth velocity	5 years	No effect
McKenzie, 1993	141	FP	Growth velocity	1 year	No effect
Ribeiro, 1993	139	BUD 400	Growth velocity	1 year	No effect
Merkus, 1993	144	BUD 600	Growth velocity	22 months	Delayed puberty in male unrelated to BUD
Agertoft, 1994	143	BUD 200–800	Height	3–6 years	No effect
Doull, 1995	152	BDP 400	Height Free urinary cortisol	7 months	↓ Growth No effect on HPAA
Konig, 1996	146	FP 100–200	Height	1 year	No effect
Price, 1997	145	FP 100	Growth velocity	>1 year	No effect
Heuck, 1997	150	BUD 800 (spacer)	Knemometry ICTP, PIIINP	4 weeks	↓ Growth velocity and collagen turnover
Simons, 1997	153	BDP 400	Linear growth	1 year	↓ Growth
Wolthers, 1997	151	FP 200 BDP 400, 800	Knemometry, ICTP, PICP, PIIINP, free urinary cortisol	2 weeks	↓ Growth and collagen turnove with BDP No effect on HPAA

Until 1980, the only objective measurement of children's growth was long-term height measurement, which is imprecise in the short term and may be affected by a wide individual variability. In 1980, *knemometry* was introduced (135). This method measures the length of lower legs and is able to detect minimal changes, even within days. Therefore, knemometry is presently considered a reliable method for short-term assessment of growth and growth velocity.

When evaluating the effects of ICS on growth, we must keep in mind that the main outcome is the final (expected) height, rather than the growth speed by itself. In fact, the clinical studies evaluating the long-term growth of children taking BUD or BDP did not demonstrate impairment of the final height (85, 73, 136–140). Moreover, FP 200 μg/day did not affect long-term growth (141); growth retardation was seen only in children taking oral steroids (142). In two separate studies, Agertoft & Pedersen (143) and Merkus et al. (144) found that BUD did not affect growth velocity or long-term statural growth. FP at doses of 50–200 μg/day did not impair long-term growth (145, 146). On the other hand, Wolthers & Pedersen (147, 148) reported a significant reduction of short-term growth with BUD 800 μg/day, but not with 400 μg/day, and similar results were obtained by Agertoft & Pedersen (79). In another study, FP 200 μg/day did not affect knemometric growth, while BDP 400 and 800 μg/day did so (149). BUD (800 μg/day) impaired growth velocity as measured by knemometry, and the impairment correlated well with the suppression of types I and III collagen turnover (150). Superimposable results were obtained in a similar study with BDP 400 and 800 μg/day (151). Significant growth reduction was reported by Doull et al. in prepuberal children receiving inhaled BDP (152). Similarly, in a recent double-blind, placebo-controlled study (153), a reduction of linear growth was observed in children treated for 1 year with BDP 400 μg/daily. By contrast, a recent meta-analysis study including 21 trials concluded that long-term BDP did not exert a significant effect on the attained height (compared to the expected) in children (154).

The available data suggest that short-term growth may be affected by high doses of ICS, but growth velocity and stature seem to depend strictly on the degree of asthma control. In fact, asthmatic children receiving ICS seem to reach their predicted height eventually. Nevertheless, this potential systemic side-effect imposes cautious use in children: the lowest effective dose must be used, and stature should be regularly monitored.

Local side-effects

Unwanted effects of the topical administration of ICS are usually defined as "local side-effects", and they include oropharyngeal candidiasis, dysphonia, cough/bronchospasm, and, rarely, contact allergy. The active principles themselves, rather than the excipients, seem to be responsible for these events (155–157). Occasionally, side-effects have also been attributed to the excipients (158). The prevalence of local side-effects depends upon several factors: inhalation technique, use of spacer chambers, the chemical characteristics of the drugs, the type of excipient, and the duration and dosage of treatment (31, 33, 155). Although a frequent topic of speculation, there is no evidence of increased risk of viral infections in patients taking ICS (159).

Candidiasis

Oropharyngeal candidiasis is probably due to a compromise of local immune responses caused by ICS (157); in fact, the immunosuppressant action of corticosteroids has been well documented both *in vitro* and *in vivo*. In assessing studies, simple colonization (i.e., positive culture without signs or symptoms) should be distinguished from the true infection (positive culture with local signs and symptoms); this fact may affect the interpretation of experimental data.

In adult patients treated with BDP up to 800 μg/day and for less than 6 months, the occurrence of *Candida* colonization (40% of subjects) did not significantly differ from that observed in control groups, whereas clinical infection was observed in about 5% of cases (160–164). The rate increased with higher doses and during long-term treatment (up to 77% of patients) (165, 166). Candidal infection in children, also on long-term BDP, is generally lower than in adults, but it increases when the daily dose exceeds 800 μg (167–169). In one study, BDP (up to 2000 μg/day) was associated with candidiasis in 3–4% of patients when employed for less than 3 months; the percentage rose to 40% after 1 year of treatment (169, 170). Sparse data are available for FLU and BUD (171–174). Three cases of oesophageal candidiasis have been described (171). In a study with FLU (1600 μg/day), the occurrence of oropharyngeal candidiasis was lower with a twice daily regimen than with q.i.d. administration (172). High-volume spacers seem to reduce both colonization and infection rates markedly (173–175).

Dysphonia

Dysphonia (alone or in association with sore throat) is an important local side-effect observed with long-term treatment with ICS. It is usually unrelated to oral candidiasis (156, 157). Dysphonia is probably the result of a nonspecific myopathy of the laryngeal muscles similar to that observed in hypothyroidism (176, 177). Dysphonia has been reported to occur with a frequency of 20–50% of adult patients consuming less than BDP 600 μg/day and up to 72% for doses up of 1600 μg/day or more (156, 160, 167, 177). As far as BUD and FLU

are concerned, the experimental results are sparse and controversial, but they agree on the dose-dependency of the side-effects (156, 173, 174).

Dysphonia seems to be due to the active drug rather than to propellants or excipients. Rinsing the mouth after inhalation and reducing the dose appear to be reasonable precautions. The use of spacers cannot be considered an effective preventive measure, but specific studies on this particular topic, and also on the reversibility of dysphonia, are still lacking.

Cough and bronchospasm

These unwanted effects seem to be strictly related to bronchial hyperreactivity (178, 179). They appear to be due to propellants (179, 180) rather than to active principles (158). With BDP, cough alone has been reported to occur in 30–40% of cases, while cough and bronchospasm occur in about 20% of patients (155, 181); deep-inspiration-induced bronchospasm has been proposed as a possible pathogenic mechanism (182). Only sparse reports are available for BUD (183), and this side-effect is usually described as of minor relevance. Cough and bronchospasm can be avoided or minimized by premedication with β_2-agonists or, preferably, by using powdered preparation rather than pressurized aerosols.

Contact allergy

Episodes of perioral eczema and mucosal oedema have been reported, but only with BUD (184–189). In some cases, positive patch tests for BUD, and not the excipients, have been described, suggesting a type IV hypersensitivity reaction (185–187). In two cases, a concomitant patch positivity to other substances was described (188, 189). Contact allergy occurs only occasionally and must be considered a very rare side-effect.

In conclusion, oropharyngeal candidiasis may occur in prolonged treatments, but simple precautions (using spacer and rinsing mouth) can minimize this adverse event. On the other hand, dysphonia may represent a troublesome side-effect, usually requiring treatment discontinuation.

Other systemic side-effects

Side-effects that are well known to occur with systemic steroids have also been sporadically described with ICS. Insomnia, hyperactivity, aggressiveness, and depression have been described in seven patients on inhaled BUD (190–192); these effects occurred in the early days and disappeared after discontinuation. No predictive parameter is known for psychic effects (193).

It is known that long-term treatment with systemic steroids may induce an increased risk of posterior subcapsular cataract or open-angle glaucoma; these side-effects are very rare with ICS (194). The safety of ICS for the eye has been well documented in children in two studies (195, 196), in which the use of ICS was not associated with an increased risk of cataract formation. Another large prospective study in adults (197), including long-term treatments and a wide range of doses, excluded the risk of cataract. A slightly increased risk of glaucoma was found in a population of patients (age >65 years) receiving high doses of ICS (198). So far, a single case of open-angle glaucoma and one of cataract have been reported with high-dose BDP in long-term treatment (199, 200).

Skin thinning and increased capillary fragility may occur in the elderly, especially women, who use high doses of ICS for long periods (201, 202). A questionnaire-based study reported that skin problems occur frequently in about 6% of patients (203). This observation is of speculative interest; nevertheless, long-term survey studies are needed for a practical measure of the problem. In addition, one case of angina bullosa haemorrhagica (204, 205) and four cases of acne have been reported (206).

No significant effect on glucose metabolism has been shown for ICS, even with high doses (up to 2000 μg) of BDP (207–209). In one study performed in asthmatic children, BUD (800 μg/day) was reported to increase HDL-cholesterol levels in a subset of subjects, but no significant changes in total cholesterol were observed (210).

An increase in neutrophil counts in the peripheral blood of patients taking ICS has been noted (211). Similar effects have been sporadically described with BDP up to 1600 μg/day, but the clinical relevance of this effect is questionable (212). BUD at high doses (1600 μg) caused a reduction of hypodense eosinophils in peripheral blood (213). Finally, in a recent study on children, BDP (600 μg/day or more) did not affect cellular immunity parameters (T and B cells and IL-2 secretion) and did not increase the risk of infections (214).

In conclusion, the safety of ICS for the eye seems to be substantiated, and no significant effect on lipid and glucose metabolism is to be expected. Some caution has to be exercised in the elderly taking high doses of ICS for long periods, since skin thinning and increased capillary fragility may occur in a low percentage of patients.

Safety of ICS in pregnancy and lactation

Uncontrolled asthma may per se constitute a risk of foetal hypoxemia with subsequent increased rate of perinatal death; furthermore, it may aggravate gestative hypertension and eclampsia (215–217). Therefore, the correct treatment of asthma in pregnant women should be the most important therapeutic aim.

As far as corticosteroids are concerned, some risk of teratogenicity has been evidenced only in animal models (cleft palate in rats) with BDP and TA (218, 219); nevertheless, no actual teratogenicity in man has ever been reported. There are sparse experimental and controlled data on the safety of ICS in pregnant women, obviously due to the ethical limitations which such studies impose. Some data are available for BDP administered to asthmatic pregnant women (220, 221): the drug appeared to have no effect on the pregnancy's outcome and not to increase the risk to the foetus. The increased rate of prematurity and low birth weight were probably due to the effects of asthma itself rather than to ICS (222). On the basis of clinical experience and the available data, BDP has been proposed as the ICS of choice for treating asthma in pregnancy (223, 224). Concerning the risks for pregnancy, the US Food and Drug Administration (FDA) classifies BDP, BUD, and FLU as class C (''risk cannot be ruled out; human studies are lacking and animal studies are positive or lacking as well''), and TA as class D (''positive evidence of risk; investigational or postmarketing data show risk to the foetus'') (223). No specific study has been conducted on ICS and lactation. Based on pharmacokinetic data, BDP can be excreted in milk; nevertheless, the therapeutic doses employed are not expected to result in significantly high concentrations (225, 226). The risks of uncontrolled asthma in pregnancy are well recognized, as is the efficacy of ICS. Therefore, it is advisable to treat asthma optimally in pregnant women; when indicated, ICS should be used at the lowest effective dose. BDP, for which more data are available, should be preferred.

Nasal corticosteroids

Nasal corticosteroids are mainly used for the management of rhinitis, but surprisingly few objective data on their safety are available. As the dosage used intranasally is low compared to inhaled corticosteroids for asthma therapy, it may be expected that the risk of systemic adverse effects is correspondingly reduced. However, the absorption dynamics from the nose and the bronchi have not been studied so far, so that this conclusion cannot be easily drawn. Furthermore, there is presently an increasing clinical indication for the combined use of corticosteroids in rhinitis and bronchial asthma, as these diseases are often associated; thus, additive side-effects due to the drugs may occur. Local side-effects such as crusting and epistaxis have also been discussed and may partially be due to the use of Freon propellants in former years.

Systemic side-effects (Table 5)

BDP was introduced about two decades ago first as pressurized intranasal spray, then as aqueous suspension, and very recently as unpressurized powder: many clinical studies and patient evaluations have been done since then. A 30-year review of the available literature was recently provided by Edelman & van Os (227). Intranasal doses of up to 400 μg a day have not been associated with suppression of the HPAA when given for up to 6 months. Only one case of adrenal suppression has been reported in the literature. Furthermore, doses of 400 μg/day or less of BDP have not been associated with osteoporosis or risk of fractures, and one study in children with seasonal allergic rhinitis did not show any effect of intranasal BDP on bone metabolism. In seven studies, including 762 patients treated with BDP up to 400 μg per day for at least 12 weeks, none of the patients had positive *Candida* cultures from the nose or clinical manifestations of *Candida* infection. In some case reports of posterior subcapsular cataracts, the majority of patients either had used BDP for more than 5 years (often exceeding the recommended dosages), or had received systemic corticosteroids. Moreover, the development of ocular hypertension or open-angle glaucoma after intranasal corticosteroid use was limited to two patients, in whom the pressure returned to normal after the discontinuation of BDP. In a recent case control study involving nearly 10 000 patients, the authors reported no increased risk of ocular hypertension or open-angle glaucoma even after high doses of nasal corticosteroids (more than 200 μg FP or more than 400 μg BDP, BUD, or TA daily) (196).

In a comparative trial involving terfenadine and nasal FP (200 μg/day), the morning plasma cortisol concentration was assessed and no effect on this parameter was demonstrated (228). Treatment of seasonal allergic rhinitis with once-daily intranasal FP in children for 4 weeks did not affect the 24-h urinary excretion of free cortisol and 17-ketogenic steroids compared to placebo (229). In a third study, nasal FP (200 μg twice daily) was demonstrated not to affect urinary cortisol levels (230). In a placebo-controlled study in patients with perennial rhinitis, the administration of 200 μg once daily FP for 1 year did not affect bone mineral density or biochemical markers of bone turnover, it did not significantly affect the HPAA, and lastly there was no evidence of posterior subcapsular cataract or glaucoma (231). A 12-month double-blind, placebo-controlled study in patients with perennial allergic rhinitis showed that FP provoked no change in nasal epithelium (assessed by biopsy) and did not modify the plasma and urinary cortisol level (232). In an open 12-month study with 400 μg BUD or BDP per day, no significant change in haematology, blood chemistry parameters, or plasma cortisol levels was found (233). Intranasal BUD (200–400 μg/day) administered for 1 year was seen not to cause either mucosal atrophy or HPAA impairment (234). Similarly, in a study lasting up to 5.5 years, the continued use of BUD had no measurable effect on the

Table 5. Systemic side-effects of nasal corticosteroids

Author, year	Ref.	A/C	No. of patients	Drug Dose μg/day	Duration	Assessment	Results
Lindqvist, 1986	234	A	104	BUD 200–400	1 year	Plasma cortisol ACTH test	No effect
Pipkorn, 1988	235	A	24	BUD 400	5.5 years	Plasma cortisol ACTH test	No effect
Tinkelmann, 1990	239	A	189	TA 250	4 weeks	Plasma cortisol	No effect
Spector, 1990	240	A	205	TA 200	12 weeks	Plasma cortisol	No effect
Feiss, 1992	238	A	62	TA 110, 220, 440	6 weeks	ACTH test	No effect
Wolthers, 1993	246	C	44	BUD 200	6 weeks	Knemometry	↓ Growth velocity
Wolthers, 1994	245	C	38	BUD 200, 400	4 weeks	Knemometry	No effect
Welch, 1994	237	A	93	TA 110, 220, 440	1 year	Plasma cortisol	No effect
Gulant, 1994	229	C	249	FP 200	4 weeks	Free urinary cortisol Plasma cortisol	No effect
Howland, 1996	231	A	32	FP 200	1 year	Bone mass density Free urinary cortisol	No effect
Howland, 1996	236	A	64	TA 110–220	6 weeks	Plasma cortisol ACTH test	No effect
Foresi, 1996	230	A	50	FP 200	8 weeks	Free urinary cortisol	No effect
Synnerstad, 1996	233	A	24	BUD/BDP 200	1 yr	Plasma cortisol	No effect
Bronsky, 1996	228	A	348	FP 200	4 weeks	Plasma cortisol	No effect
Brannan, 1996	248	A	25	MF 200–4000	Single dose	Cortisol AUC	No effect
Wihl, 1997	242	A	14	BUD/BDP 200, 400, 800	Single dose and 4 days	Plasma cortisol Free urinary cortisol	Single dose: no effect on plasma cortisols ↓ urinary BUD Multiple dose: ↓ urinary cortisol, dose-dependent
Brannan, 1997	249	A	64	MF 200–400	36 days	ACTH test	No effect
Brannan, 1998	250	C	96	MF 50, 100, 200	7 days	Plasma cortisol	No effect
Holm, 1998	232	A	42	FP 200	1 year	Plasma cortisol	No effect
Wilson, 1998	243	A	60	FP 200 TA 220 BDP 336	4 days	Free urinary cortisol ACTH test	Only FP ↓ urinary cortisol No other effect
Wilson, 1998	241	A	20	BUD 200, MF 200 TA 220	5 days each	Plasma/urinary cortisol, osteocalcin, eosinophils	No effect
Rachelefsky, 1998	244	C		BDP 168	1 year	Free urinary cortisol Height	No effect on HPAA ↓ Growth

* Adult/child.

HPAA and did not alter nasal epithelium (235). The possible side-effects of TA (110 or 220 μg/day) aqueous nasal spray and oral prednisone on the HPAA were assessed in a study of male rhinitic subjects (236). Morning plasma cortisol level, urinary cortisol, and ACTH stimulus were evaluated, and no significant effect of the nasal corticosteroid on these parameters was found. No meaningful changes of morning serum cortisol levels were recorded in 93 patients with allergic rhinitis taking TA (110, 220, and 440 μg/day) for more than 1 year (237). The lack of effects on the HPAA by TA was further confirmed in three medium-term studies on adult patients (238–240). In a recent crossover controlled study (241), 5-day courses of BUD, MF, and TA at clinically recommended doses did not affect the HPAA, bone metabolism, or blood white cells.

However, some measurable effects of nasal corticosteroids have also been reported. Wihl et al. reported that BUD 400 and 800 μg single dose (but not BDP) affected urinary cortisol; the data were confirmed with the same drugs after a 4-day course (242). In a recent study conducted in healthy volunteers with a 4-day course of different nasal steroids, FP (200 μg/day μg/day), but not TA (220 μg/day) or BDP (336 μg/day), affected overnight urinary cortisol; on the other hand, none of the drugs affected serum cortisol and the ACTH response (243). Beclomethasone nasal spray (mean dose 168 μg b.i.d.) up to 12 months was reported not to affect the HPAA; nevertheless it exerted a small but significant effect on the growth of children aged 6–9 years (244). By means of knemometry, Wolthers & Pedersen demonstrated that 4-week treatment with intranasal BUD (200 or 400 μg/day) did not significantly affect growth velocity, although a trend toward reduction was seen with 400 μg/day (245). However, in another study comparing terfenadine 60 mg/day, budesonide 200 μg/day, and depot methylprednisolone 60 mg, a significant reduction of growth velocity was seen over 6 weeks in those children receiving nasal and systemic steroids (246).

A recent review summarized more than 20 clinical trials involving more than 6000 patients treated with

MF, concluding that there was no detectable effect on the HPAA (247). In particular, Brannan et al. in two studies found that nasal MF did not affect the adrenal function either in a single dose up to 4000 μg (248) or in a 36-day course (200–400 μg/day) (249). Nor was an effect on HPAA in children detectable with MF (50, 100, or 200 μg/day) in a 7-day course of therapy (250). Finally, a single case of hyperactivity and disturbed behaviour after nasal BDP has been so far described (251). In summary, intranasal corticosteroids are highly effective; nevertheless, they are not completely devoid of systemic effects. Thus, care has to be taken, especially in children, when long-term treatments are prescribed.

Local side-effects

Again, the longest experience of local side-effects is available for BDP (227). Since local application of corticosteroids may cause dermal atrophy, the possibility of mucosal atrophy by long-term use of intranasal steroids has been thoroughly investigated. In several studies, including chronic use of intranasal BDP for periods of up to 36 months, biopsy investigations did not show any effect on nasal mucosa. The safety of once-daily administration of 220 μg/day of TA for 3 weeks was evaluated in 429 patients with seasonal allergic rhinitis compared to the placebo group, showing no significant difference between the two groups (252). Similar results were obtained in a multicenter study evaluating the safety of a once-a-day regimen of 110, 220, and 440 μg TA administered to patients with perennial allergic rhinitis, aged 12–65 years (253). A further study of adult patients with perennial allergic rhinitis treated for 12 months with MF (200 μg/day) showed in nasal biopsies no adverse tissue change after treatment (254). Similarly, no significant effect of MF (200 μg/day) on mucociliary clearance and olfactory function was detectable (255). The data further indicated that some of the adverse events such as irritation, crusting, itching, and stinging may be due to the propellant used in older formulations rather than to the active drug. Epistaxis (including blood-containing secretions) was in some studies reported to be more frequent (about 15%) in the active than in the control group (227, 256); in other studies, it was not (257, 258). It is advisable that patients on long-term therapy have their nasal mucosa periodically examined; such patients may use an inert ointment after the use of the steroid to protect mucosa from drying. The application once daily of intranasal steroids may possibly reduce these minor side-effects.

In conclusion, although the available studies on intranasal steroids show favourable results, local side-effects could be reduced by teaching the right application technique. Long-term use should be periodically monitored.

Conclusions

ICS are presently the most effective drugs for the treatment of bronchial asthma (1–4), since they dramatically reduce the inflammatory phenomena underlying the disease; similarly, nasal corticosteroids are a first-choice treatment for rhinitis (259). ICS exert their effects by acting on several components of inflammation and they modify the anatomopathologic features of the inflammatory process in most cases. For these reasons, ICS are widely used and prescribed in both adults and children, usually in long-term treatments. Therefore, the safety of these drugs is of importance for both general practitioners and specialists.

According to the available controlled studies, some effects on the HPAA and bone metabolism are detectable with high doses of ICS. Indeed, the effects on the HPAA and bone metabolism are measurable only by means of biochemical parameters; their clinical significance is still unknown and is probably extremely small compared to the benefit achieved. With regard to children's growth, some data suggest that short-term growth can be affected by high doses of ICS, but this effect is certainly less significant than that due to uncontrolled asthma. It is often difficult to separate the effects of asthma and ICS. Stature and growth velocity seem to depend mainly on the degree of asthma control (134, 260), and children receiving ICS seem to reach eventually their predicted height. Nevertheless, the potential of systemic side-effects imposes, especially in children, a cautious use: it is advisable to use the lowest effective dose and, when an MDI is used, it should be in combination with a large-volume spacer.

Some local side-effects have also been described. Oral candidiasis seems to be dose-related and can be minimized by using spacers and rinsing the mouth after inhalation, whereas dysphonia, if troublesome, may require discontinuation of treatment. Other systemic side-effects have also been described: cutaneous side-effects may be of some relevance in the elderly, whereas neurologic and ocular adverse events have to be considered anecdotal.

ICS, together with avoidance of trigger factors and use of rescue bronchodilators, remain the first-choice therapeutic option for the management of bronchial asthma, and their risk/benefit ratio is, overall, favourable. This does not imply that ICS are totally safe: in fact, a class relabelling for ICS has been recently approved in the USA (261, 262), and the British Committee on Safety of Medicines (CSM) (263) has also emphasized some warnings. A careful evaluation of patients (especially those taking high doses for long periods) is always required. Similar considerations are valid also for nasal corticosteroids: the risk/benefit ratio is generally favourable, but special caution has to be exercised in children, since systemic side-effects have been described.

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