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EDITORIAL

Is long-term treatment with inhaled steroids in adults hazardous?

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Since the introduction of inhaled steroids for the treatment of asthma, numerous studies have shown that they have an advantageous therapeutic index in relation to oral steroids, as well as high potency. They certainly represent a major advance in asthma treatment.

Initially, inhaled steroids were used in moderate doses and primarily as a substitute for oral steroids. In recent years we have seen a tendency to prescribe inhaled steroids in higher doses than previously used [1, 2]. They have also been advocated in low doses at an earlier stage in the treatment [2, 3]. If steroids are to be used at an earlier stage in asthmatics with relatively mild symptoms, any significant side-effect must be considered on its own, rather than being compared with the side-effects of oral steroids. The question of how harmless the treatment with topical steroids is must be raised.

Local side-effects

The most important side-effects previously reported in the case of inhaled steroids in commonly recommended doses are oropharyngeal candidiasis and dysphonia [4]. The reported incidence of candidiasis varies considerably, from 3 to 77%, and this is largely dependent on the diagnostic criteria which are used. The occurrence also seems to be related to the dose and frequency of inhaled steroids and to the type of inhaler.

The use of spacers and induced gargling are reported to reduce the occurrence of oropharyngeal candidiasis [5].

Hoarseness or dysphonia, on the other hand, may affect the patient in a more significant way, although severe dysphonia is a relatively rare occurrence. It may represent a local steroid myopathy [6], and it is related to vocal stress [7]. Even in the case of dysphonia, the frequency of this side-effect appears to be related to the dose [6, 8], and it generally disappears following drug withdrawal [6, 9].

There is currently no evidence to indicate that inhaled steroids increase the incidence of respiratory infections [10] or induce atrophic changes in the airway mucosa [11, 12]. Topical treatment with inhaled steroids may induce a mild cough and wheezing [6, 13], but these symptoms can usually be avoided if a bronchodilating drug is inhaled prior to steroid inhalation [14]. An exacerbation of asthma has been reported as a rare problem in conjunction with inhaled steroids [15, 16].

Overall, the local side-effects of inhaled steroid treatment do not appear to represent a hazard to the patient, assuming that patients and their physicians are aware of side-effects and adapt the treatment strategy accordingly.

Systemic side-effects

There are good reasons for being more concerned about the possible systemic side-effects of inhaled steroids. They are rapidly and extensively absorbed from the upper and lower respiratory tracts and the gut. However, both of the most commonly used inhaled steroids, budesonide (BUD) and beclomethasone dipropionate (BDP), are rapidly biotransformed to less active metabolites and only a minor part reaches the systemic circulation in bioactive form. Even so, both drugs may have systemic effects if given in high enough doses. The question is whether these effects are of any clinical significance.

In daily doses of up to 800–1,200 μg, the effect on plasma cortisol is small or insignificant [9]. Nevertheless, when given in higher doses both drugs may have systemic effects.

Adrenal suppression

Adrenal suppression has been reported when the daily dosage exceeds 1,500 μg [17, 18] and it has been suggested that at higher doses BUD had significantly less effect on plasma cortisol than BDP [19]. Inhaled steroids have also been shown to impair the tetracosactrin stimulation test of adrenal function [20]. This effect was more frequently seen in patients who had previously been treated with oral steroids. On the basis of their findings, Brown *et al.* [20] recommended that screening tests of the hypothalamus-pituitary-adrenal axis should be performed in all asthmatics taking >1,500 μg of inhaled steroids daily.

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Osteoporosis

Osteoporosis is a serious complication of systemic corticosteroid treatment. Long-term oral treatment affects bone turnover and density leading to increased incidence of fractures. Until recently, similar information on inhaled steroids was lacking. In recently published studies, JENNINGS *et al.* [19, 21] evaluated the effect of inhaled BUD on various indices of bone turnover in healthy volunteers. At a daily dose of <1,200 μg, BUD depressed serum osteocalcin, a marker of osteoblast activity. This effect occurred to an even greater extent with prednisolone and BDP in equivalent doses. Unlike BDP (2,500 μg) and prednisolone, BUD (3,200 μg) did not affect serum alkaline phosphatase [19]. Two other recently published studies investigated the effect of high-dose inhaled steroids on bone turnover in healthy volunteers. In the first study, ALI *et al.* [22] demonstrated that 2,000 $\mu g \cdot day^{-1}$ of BDP, given for one month, increased bone resorption, as reflected by a statistically significant rise in the urinary output of hydroxyproline, a breakdown product of the osteoid matrix. However, BUD in a dose of 1,800 μg did not increase the hydroxyproline output. In the second study, POUW *et al.* [23] showed that BDP administered for two weeks reduced the concentration of osteocalcin.

Although these studies were not blind and the number of subjects studied was small, they indicate that inhaled steroids may interfere with bone metabolism. However, we do not yet know if these effects on bone metabolism are sufficient to induce bone mass reduction/osteoporosis.

From the studies of healthy volunteers and of asthmatic children [24], it appears that BUD has less of an impact on biochemical markers than BDP. It is unlikely that asthmatics differ in this respect, but the results still need to be confirmed in adult patients. Furthermore, the clinical significance of such biochemical differences needs to be evaluated in drug studies of patients which also monitor bone density and fracture incidence.

However, the observation that inhaled steroids may influence bone metabolism and that this effect is dose-dependent, indicates that caution is needed before initiating long-term treatment with high-dose inhaled steroids.

Skin-thinning

Skin-thinning combined with spontaneous and easy bruising has been reported in conjunction with high-dose inhaled BDP [25, 26]. In this issue of the Journal, MAK *et al.* [27] report on a questionnaire survey of the prevalence and characteristics of easy bruising in patients on inhaled steroids. The authors demonstrate a significantly higher prevalence of easy bruising in respiratory patients taking inhaled steroids compared with non-respiratory patients without topical treatment. Furthermore, the patients who reported easy bruising were older, on higher doses and had been taking inhaled steroids for longer than non-bruisers. Females reported easy bruising more often than men, but males taking inhaled steroids ran a higher relative risk of bruising than females. The occurrence of easy bruising increased significantly with increasing dosage and use up to 60 months.

The clinical significance of easy bruising is unclear, but the phenomenon indicates that inhaled steroids have systemic effects. It may, therefore, represent an early marker of the resorptive effects of inhaled steroids, which indicates that systemic effects may also occur when steroids are administered in moderate doses and that these effects are dose-dependent. The fact that the prevalence of easy bruising increased with treatment time is noteworthy and indicates that long-term treatment with inhaled steroids may be more hazardous than previously assumed.

At present, inhaled steroids are used in an increasing number of patients. Their clinical efficacy has been established in numerous studies. The potential side-effects, however, are far less well-documented. It is well-established that inhaled steroids may affect biochemical markers of adrenal function and bone turnover, although the clinical significance of these effects is not yet known. The report in this issue of the Journal of easy skin bruising in patients treated with inhaled steroids indicates that the systemic effects may be more than a "biochemical finding". Consequently, some sort of restriction appears to be warranted when it comes to the unreserved use of inhaled steroids. Their clinical benefit should always be weighed against potential adverse effects, especially when long-term treatment is expected. Although their benefits in asthma treatment far outweigh their side-effects for the majority of patients, the smallest possible dose should still be used. Not only are more studies on undesirable effects of inhaled steroids, needed, but we also hope that in the future a new generation of topical steroids, undergoing a more complete degradation in the liver and circulation, will obviate our present concern about the adverse effects of these drugs.

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