

MEETING REPORT

Report of a workshop assessing the risks and benefits of inhaled

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The international guidelines on asthma management, published in 1992 [1], suggest that inhaled anti-inflammatory therapy should be initiated in mild-to-moderate asthma when, among other criteria, the patient has chronic symptoms that require almost daily use of a short-acting inhaled β_2 -agonist. The recommendations for primary therapy are the inhaled corticosteroids, sodium cromoglycate or nedocromil sodium, but which drug should be used first is left to individual choice, apart from a recommendation that all children should begin with a trial of sodium cromoglycate. A workshop was held in June 1993 in Grindelwald, Switzerland, to review the risks and benefits of inhaled anti-inflammatory therapy for asthma, that might be considered in arriving at that choice.

Safety

Dukes recounted the results of his review of World Health Organization and manufacturer's clinical safety data on sodium cromoglycate and nedocromil sodium. Despite its availability for over 20 yrs, sodium cromoglycate has not been associated with serious side-effects and remains one of the safest drugs ever developed. Nedocromil sodium is newer but appears to be following this tradition of safety [2]. The most common complaint with nedocromil sodium is a bitter taste experienced by 10–15% of patients. The potential systemic side-effects of inhaled corticosteroids on growth, bone metabolism, the hypothalamo-pituitary-adrenal (HPA) axis and skin were discussed separately at the workshop.

Pedersen and **Wolthers** reviewed their studies on the effects of budesonide and beclomethasone dipropionate (BDP) on short-term growth using knemometry, a technique which accurately measures lower leg growth over a period of weeks. Significant reductions in growth velocity were only evident during treatment with budesonide 800 $\mu\text{g}\cdot\text{day}^{-1}$, and BDP 400 $\mu\text{g}\cdot\text{day}^{-1}$. The extent to which short-term studies can be extrapolated to predict final height attained is not known, since growth naturally proceeds in lulls and spurts, and at times stops altogether;

but, they may be a fairly reliable predictor. **Pedersen** also described a long-term follow-up over approximately 4 yrs and results to date are similar to those of the knemometry studies. **Doull** described a study [3] in which his group measured actual height over a period of 6 months during treatment with BDP, 400 $\mu\text{g}\cdot\text{day}^{-1}$, in children with mild asthma, and found a highly significant reduction in growth which had not caught up in the 5 months following discontinuation of treatment. **Pedersen** concluded that in the short-term (weeks) and intermediate-term (months), budesonide at doses of ≤ 400 $\mu\text{g}\cdot\text{day}^{-1}$ *via* Nebuhaler does not have an adverse effect on growth; whereas BDP 400 $\mu\text{g}\cdot\text{day}^{-1}$ *via* Diskhaler does have a significant effect upon growth velocity. At present there are no good prospective studies evaluating long-term growth and the effect on final growth outcome, but uncontrolled asthma has a detrimental effect on growth, and this is probably the most important factor in choosing anti-inflammatory therapy.

Pedersen and other speakers stressed the importance of defining the particular corticosteroid and the delivery system, since the degree of systemic absorption depends on the pharmacokinetic properties of the drug and on the delivery device. The difference in the effect on growth between the same dose of BDP delivered *via* Diskhaler and budesonide *via* Nebuhaler may reflect differences in the amounts of drug delivered to the lung and that which is swallowed, as well as the drugs' relative bioavailabilities from the lungs and intestines. Any unchanged drug absorbed from the lungs is not subject to first-pass hepatic metabolism. For example, delivery *via* Turbuhaler has a higher clinical effect because it delivers more drug to the lungs, but also a higher systemic effect since more drug is absorbed at this site [4]. However, systemic absorption arising from the drug deposited in the mouth can be reduced by mouth washing.

Toogood reviewed the effects of inhaled corticosteroids on bone metabolism, most of the studies being with BDP and budesonide, and largely the latter. At high doses, both drugs may decrease serum levels of osteocalcin; budesonide, may inhibit procollagen production and BDP may increase urinary hydroxyproline output. These changes are subtle and their significance is unclear, although inhibition of dehydroepiandrosterone production by either drug may be important to postmenopausal asthmatic women, who depend critically upon androgen production from the adrenal cortex for their ability to biosynthesize oestrogen to restrain osteoclast activity and

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minimize bone resorption. The important outcomes are the effects on bone mineral density and prevalence of vertebral fracture. In Toogood's patients there was a reduction in bone mineral density associated with an intermediate dose (1–2 mg·day⁻¹) of inhaled corticosteroids, but the opposite was true for cumulative lifetime dosage - the higher the total dose, the higher the bone mineral density [5]. Inhaled corticosteroids probably reduce the overall risk of corticosteroid-induced osteoporosis and fracture in severe asthmatics, by diminishing oral corticosteroid intake and allowing an increase in physical activity. Again, differences exist between the inhaled corticosteroids, and the pharmacodynamics of different actions of inhaled corticosteroids on bone metabolism, and their prognostic implications for the long-term could be better defined than they are. Some subsets of asthmatic patients merit rigorous studies, for example postmenopausal women, adolescents and children.

The endocrine effects of inhaled corticosteroids, specifically upon HPA axis function, were the subject of an integrated safety study presented by **Folb**. Many of the published studies could be criticized in their methodology. A commonly used test of HPA function is to measure plasma cortisol in a single blood sample, usually taken in the morning. Cortisol levels fluctuate widely, both between and within individuals, and the value of a single random measurement was felt to be nil. Studies that measured plasma cortisol levels in blood samples taken regularly over 12 or 24 h were felt to provide the most reliable results. However, the measurement of levels of free cortisol in the urine collected over 24 h, or overnight, was thought to be a good compromise between ease of use and sensitivity. Experiences with the response to synthetic adrenocorticotrophic hormone (ACTH) (*e.g.* the short tetracosactrin test) seemed at variance. Using a good test in a large enough number of patients, it was felt that significant suppression of HPA function could be shown at 400 µg·day⁻¹ BDP or equivalent. A large-volume spacer device may help reduce effects on the HPA axis. The clinical significance of the degree of HPA axis suppression that has been demonstrated is unknown. The most obvious serious clinical consequence would be an acute adrenal crisis, but this has very rarely been reported in the literature. One asthmatic child of the eight in a study described by **TAL** [6] was experiencing clinically relevant problems on a daily dose of BDP of 450 µg·day⁻¹, and these resolved when treatment was switched to nedocromil sodium and theophylline. However, **Brown** presented his work showing that patients on high-dose inhaled corticosteroids are able to mount an appropriate cortisol stress response to acute exacerbations of their asthma.

As with most of these systemic side-effects, it appears that individual susceptibility can be quite variable, and that this may be due to differences in metabolic capacity between patients. However, routine testing for suppression of the HPA function was generally felt by the workshop to be neither important nor necessary, although physicians in litigious societies, such as the USA, might be persuaded otherwise.

There is less literature on the effect of inhaled corti-

steroids on the skin. These effects, which occur at high doses, include skin thinning and "easy" bruising (purpura), were reviewed by **Edwards**. Cutaneous atrophy is caused by reduction in total collagen content and a failure or reduction in maturation. There is a reduction in elastic tissue, loss of anchorage of the microvasculature and an antimitotic effect, which reduces epithelial thickness. Oral blood blistering, occasionally reported, may share the same mechanism. Cutaneous atrophy is dose-related and more common in the elderly, whose initial skin thickness will be less. **Mak** reported the results of a questionnaire survey among users of high-dose BDP, showing that, in the UK at least, the prevalence of easy bruising is somewhere between 40–50%. Females may be more prone to easy bruising, although males are more likely to complain of it. Preliminary data from **Mak's** group suggest that easy bruising does not correlate with adverse effects on other body systems, although **Bone** reported that the effect was serious enough in some patients to attempt weaning off high-dose inhaled corticosteroids and substituting with nedocromil sodium. **Edwards** said that the prevalence of oral blood blistering, which mainly affects the soft palate, appears to increase with duration of use of inhaled corticosteroids but can be lessened by use of a spacer device and generally good oral hygiene (*e.g.* rinsing the mouth and washing dentures).

Efficacy

The efficacy of the inhaled anti-inflammatory drugs in mild-to-moderate asthma was reviewed by **Holgate**. Inhaled corticosteroids are undisputably effective anti-inflammatory agents and clinically efficacious in treating asthma. The nonsteroidal inhaled anti-inflammatory agents, nedocromil sodium and sodium cromoglycate, are less effective overall than the inhaled corticosteroids, but some studies have indicated that they can provide control of mild-to-moderate asthma comparable with that of 400 µg·day⁻¹ of BDP [7, 8]. Nedocromil sodium appears to be more effective than sodium cromoglycate [9]. **Bone** discussed anti-inflammatory treatment for moderate-to-severe asthma, for which inhaled corticosteroids are the first-line therapy [1]. However, **Bone** pointed out that, in such patients, nedocromil sodium has been shown to be able to substitute for part of the dose of inhaled corticosteroid and to provide added benefit to an existing treatment with inhaled corticosteroid (reviewed in [10]). It may, therefore, represent a strategy to avoid the increased risk of side-effects at high doses of inhaled corticosteroid.

Pauwels discussed the treatment of chronic, severe asthma. Here, the therapeutic value of high doses of inhaled corticosteroids is well-known and the risk:benefit ratio is clearly in favour of high doses of inhaled corticosteroids, when compared with oral corticosteroids. Of all the treatments used in chronic, severe asthma, oral corticosteroids have the highest risk:benefit ratio and the first step in reducing oral corticosteroids should be to replace them, whenever possible, with high-dose inhaled corticosteroids. Nedocromil sodium has shown some potential as an oral

corticosteroid-sparing agent, and a trial with nedocromil sodium may be warranted in some patients after the dose of inhaled corticosteroid has been optimized.

Conclusion

Present evidence on the safety of low-dose inhaled corticosteroids is reassuring, although there is a need for physicians to be vigilant for the occasional patient who experiences paradoxical adverse effects at low doses. In addition, there is lack of information on whether the small changes in indices reflecting systemic effects of inhaled corticosteroids may have more serious consequences in the long-term, for example with prolonged use from childhood into later life. Some physicians may, therefore, prefer to use nedocromil sodium or sodium cromoglycate as initial primary therapy, even though overall efficacy is less well assured than it is with the more potent inhaled corticosteroids. In more severe asthma, nedocromil sodium may be useful to reduce high intake of inhaled corticosteroids, although at present there is no better alternative to high-dose inhaled corticosteroids and their side-effects are less serious than the threat of the disease itself.

Recent treatment guidelines emphasize the importance of regular monitoring, so that the control of asthma is maintained by the minimum level of medication, in order to avoid drug-induced side-effects. This means that regular attempts should be made to reduce therapy. When communicating guidelines and the stepcare approach to treatment to primary care physicians, it is important to emphasize not only the step-up in treatment but also, equally, the step-down.

Participants

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