CORRESPONDENCE

Side-effects of high-dose fluticasone propionate in children

To the Editor:

EFTHIMIOU and BARNES [1], in their review "Effect of inhaled corticosteroids on bones and growth", referred to our paper "Growth and adrenal suppression in asthmatic children treated with high dose fluticasone propionate" [2] as "anecdotal reports of growth deceleration in asthmatic children treated with inappropriately high doses (*i.e.* 5–10 times the recommended dose) of inhaled corticosteroids". In our study, the high doses were used as an alternative to oral corticosteroids in a group of children who had very severe asthma not controlled with lower doses of inhaled corticosteroids, short- and long-acting β -agonists and theophyllines. Frequent attempts were made to step down treatment if the asthma was stable. They should also be aware that the paper was not a study but a series of six case reports, and that case reporting is very important in new drug pharmacovigilance [3].

Fluticasone in doses of up to 1,000 $\mu\text{g}\cdot\text{day}^{-1}$ (five times the recommended dose) is allowed by the British Thoracic Society guidelines (1995) for the treatment of asthma in children and P.J. Barnes himself has stated that "there is no convincing evidence that inhaled steroids even in high dose (2 $\text{mg}\cdot\text{day}^{-1}$) have effects on ... growth in children" [4].

We conducted a survey of inhaled corticosteroid prescriptions in primary care and found that >30% of all prescriptions for fluticasone are in excess of recommended doses and 4% for $\geq 1,000 \mu\text{g}\cdot\text{day}^{-1}$ (C. Fitzpatrick, personal communication). A survey of specialist paediatric centres in the UK showed that when high doses of inhaled corticosteroids ($>1,000 \mu\text{g}\cdot\text{day}^{-1}$) are thought necessary, nearly all choose fluticasone propionate (W. Lenny, personal communication). Thus, the usage of fluticasone propionate in high doses in severely asthmatic children is common and not confined to our practice.

There are no long-term studies looking at this newest inhaled corticosteroid in high doses, hence the importance of our case reporting, which J. Efthimiou and P.J. Barnes underestimate.

All of our cases demonstrated that a very high first-pass hepatic metabolism (99.9%) for fluticasone does not prevent the occurrence of serious systemic effects at high doses ($\geq 1,000 \mu\text{g}\cdot\text{day}^{-1}$). This is probably due to the very high lipophilicity of fluticasone (250–300-times greater than beclomethasone or budesonide), which results in a much higher tissue distribution, longer plasma half-life and greater glucocorticoid receptor affinity than budesonide or beclomethasone [5]. Fluticasone is the only inhaled steroid reported to accumulate with repeated $>1,000 \mu\text{g}\cdot\text{day}^{-1}$ dosing in adults [6–11], although no accumulation effect has been detected with a dosage of 400 $\mu\text{g}\cdot\text{day}^{-1}$ in children [12].

Therefore, there is also good pharmacokinetic evidence to support our clinical observations and these factors, in the

absence of studies, should be taken into account when choosing an inhaled corticosteroid at a high dose in severely asthmatic children.

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REPLY

From the authors:

Case reports such as those reported by TODD *et al.* [1] may be of some value in that they indicate that a few sensitive patients treated with high doses of inhaled steroids may experience a reduction in growth velocity. As stated in our review [2], identifying these patients, by means of their phenotypic and genotypic characteristics, may be key to managing paediatric asthma safely and optimally in the future.

The six case reports describe children receiving high doses (up to >10 times those recommended) of inhaled corticosteroids [1]. However, they provide only limited information on a number of key questions, namely: the control of the patients' asthma and the need for a change in treatment, their total corticosteroid exposure, the reason for the high doses of fluticasone propionate (FP) selected, the few height measurements and their precise timing with regard to both inhaled and oral corticosteroid therapy, details of other concurrent asthma medication and other diseases which could contribute to slowing of growth, the reason for continuing high doses of FP (up to 2,250 $\mu\text{g}\cdot\text{day}^{-1}$) for long periods and the lack of control patients, which have already largely been highlighted by others [3, 4]. It seems very likely that the growth reduction reported in these cases may be equally explained by any or a combination of these other important clinical factors and not predominantly by FP as suggested in the article.

The case reports also need to be interpreted in the context of all the relevant major clinical trials in order to adequately assess the important risk–benefit balance of inhaled steroids in the treatment of children with asthma. At least three randomized, controlled studies have demonstrated that FP used at recommended doses up to 200 $\mu\text{g}\cdot\text{day}^{-1}$ for at least 1 yr has no significant effect on growth velocity [5–7]. In addition, a further study in pre-pubertal children with asthma maintained on beclomethasone dipropionate (BDP) or budesonide in doses between 200 and 400 $\mu\text{g}\cdot\text{day}^{-1}$, showed that when children with suppressed growth were changed to treatment with FP 100–200 $\mu\text{g}\cdot\text{day}^{-1}$ for 1 yr, during which asthma control was well maintained, their mean height velocity standard deviation scores increased substantially (*i.e.* from -1.7 on BDP and -1.0 on budesonide, to +1.6 on FP) [8].

FP in doses up to 1,000 $\mu\text{g}\cdot\text{day}^{-1}$ is recommended by the British Thoracic Society guidelines in children with severe asthma, who might otherwise require treatment with oral corticosteroids [9]. The observation that most respiratory paediatricians choose to use FP as opposed to other inhaled steroids, when high doses of inhaled steroids are necessary, lends further support to the relative confidence specialists have in prescribing FP in children with severe asthma, based on their own clinical experience. This confidence must also arise from the substantial number of large, randomized, controlled clinical trials which have demonstrated that FP is at least as or significantly more effective at half the milligram dose, with the same or significantly

less systemic activity than BDP or budesonide, as recently summarized in a comparative meta-analysis [10].

The study by WHITAKER *et al.* [8] also confirms the 2:1 potency ratio of FP compared with BDP and budesonide and indicates that at therapeutically equivalent doses, if substituted for BDP or budesonide, FP may allow catch-up growth to occur in children with suppressed growth. At higher than currently recommended doses, bearing in mind the need for only half the daily milligram dose of FP compared with other inhaled steroids, there is no reason to expect otherwise. Indeed, a recently completed prospective, randomized study, comparing FP 400 $\mu\text{g}\cdot\text{day}^{-1}$ with BDP 400 $\mu\text{g}\cdot\text{day}^{-1}$ over 1 yr, in 342 moderate-to-severe asthmatic children requiring treatment with inhaled corticosteroids, demonstrated that growth velocity was significantly greater on FP, in addition to significantly better lung function control [11].

The low systemic activity of FP is related to both its high first-pass metabolism and its low oral absorption, leading to its very low oral bioavailability of <1%, which is substantially less than with other inhaled steroids [12]. The suggestion that FP accumulates after repeat dosing any more than any other inhaled steroid is neither pharmacokinetically consistent nor substantiated clinically. Although the terminal elimination half-life of FP is longer than other inhaled steroids, for equal amounts of drug absorbed, the resulting steady-state concentrations are likely to be very similar, consistent with the fact that the extent of accumulation is independent of the half-life of the drug and is only a function of clearance [13]. As G.R.G. Todd points out, no accumulation effect has been detected with FP at doses of 400 $\mu\text{g}\cdot\text{day}^{-1}$ in children [14].

The only effective alternative to high-dose inhaled steroid therapy in children with severe asthma is frequent courses or maintenance therapy with oral corticosteroids, the systemic activity and effect on growth of which are likely to be substantially greater than therapeutically equivalent doses of inhaled steroids. With its high therapeutic ratio, FP currently offers one of the best risk–benefit options for the treatment of children with moderate-to-severe asthma, as confirmed by a number of randomized, controlled clinical studies [11, 15, 16].

Currently the most reliable way of assessing the effect of inhaled steroids on growth in children is through well-designed, carefully monitored, prospective studies, using standardized stadiometers and experienced staff, conducted over periods of at least 1 yr. Such data as they currently exist suggest that inhaled steroids at recommended doses have little if any effect on growth in children [2]. In addition, no effect on final height has been convincingly demonstrated with inhaled steroids and further appropriately designed studies, particularly with higher doses, are required to determine what, if any, this effect is. Inhaled steroids currently offer the best balance of risk–benefit ratio in the treatment of children with moderate-to-severe asthma, but the dose should be monitored closely with the aim of reducing this to the minimum required to provide effective control, with regular height measurements, bearing in mind that severe asthma itself can suppress growth.

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