When inhaled corticosteroid therapy (ICT) was introduced to clinical practice thirty years ago, it appeared to be both effective and safe.\(^1\,2\) There was no evidence of adrenal suppression at the recommended doses\(^3\,4\) and when oral corticosteroids were replaced by ICT, adrenal function recovered.\(^5\) It must be added that there were reports of adrenal atrophy on ICT,\(^6\) as the first drug of choice for the prophylaxis of asthma, but over the years the importance of such doses was not supported by the literature on ICT, which suggests a rather flat dose response curve for all types of ICT; even in studies in which the degree of compliance was high, the swallowed portion, representing the major part of the administered dose,\(^6\) is almost entirely destroyed on first pass hepatic metabolism,\(^7\,8\) and the drug's high receptor affinity and prolonged dissociation half life\(^9\) make it apparently ideal for use by intermittent inhalation.\(^10\) Early studies demonstrated the safety and efficacy of FP given to asthmatic children in doses of 100 to 200 µg per day,\(^11\) and numerous later studies confirmed these early impressions.\(^12\,13\) Even at high doses, it was apparently no more toxic than beclomethasone.\(^14\) So what went wrong? In particular, has the pharmacology of FP been inadequately investigated? Hardly: a search of PubMed in August 2002 generated 795 papers on the pharmacology of FP and 208 on its adrenal effects. We know a great deal about FP, its pharmacology, and 208 on its adrenal effects. We know a great deal about FP, its pharmacology, and not only did ICT gradually supplant sodium cromoglycate (cromolyn) as the first drug of choice for the prophylaxis of asthma, but over the years paediatricians began to follow their adult colleagues\(^16\) in prescribing greater than licensed doses of ICT. The use of such doses was not supported by the literature on ICT, which suggests a rather flat dose response curve for all types of ICT; even in studies in which the degree of compliance was high, the swallowed portion, representing the major part of the administered dose,\(^6\) is almost entirely destroyed on first pass hepatic metabolism,\(^7\,8\) and the drug's high receptor affinity and prolonged dissociation half life\(^9\) make it apparently ideal for use by intermittent inhalation.\(^10\) Early studies demonstrated the safety and efficacy of FP given to asthmatic children in doses of 100 to 200 µg per day,\(^11\) and numerous later studies confirmed these early impressions.\(^12\,13\) Even at high doses, it was apparently no more toxic than beclomethasone.\(^14\)

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Other factors play a part in determining the systemic effects of ICT. Inhaler technique and compliance are clearly of major importance. Children frequently use holding chambers (spacers) that increase intrapulmonary deposition and efficacy\(^17\,18\) and will also enhance systemic absorption. The lung deposition of inhaled drugs increases with age,\(^19\) so the minimum effective dose may actually decrease as the child gets older. Systemic absorption is appreciably greater in normal volunteers than in asthmatic patients,\(^20\) which may explain why some non-asthmatics appeared in Todd's survey. Although as we have seen extrapolation is a dangerous pastime, it is reasonable to speculate that systemic absorption will increase as asthma comes under control, further emphasizing the need to step doses down as well as up. It is however clear that the systemic dose of ICT bears only a passing resemblance to the administered dose, and will vary greatly between children and indeed in the same child from time to time. It is therefore impossible to state with certainty that one particular dose is safe while another is not. There is certainly no point in complicating the issue by expressing ICT doses in relation to weight or body surface area. What can be said with considerable certainty is that the optimum dose is the lowest effective dose, and that this dose will vary from time to time, and with the age of the child, the inhaler device used, and the degree of compliance.

What are the implications for the practising clinician? The findings of this survey cannot be ignored, but nor should they be used as an excuse for a further outbreak of steroid phobia. Nevertheless, there are implications both for patients already on high-dose FP, and for those for whom this therapy is contemplated.

Patients who are currently on high dose FP should remain on it, and they should be advised that this is a much safer option than suddenly discontinuing treatment. However, it would seem sensible to try to identify those few individuals in whom adrenal suppression has occurred by assessing adrenal function. My suggestion would be that children on FP in doses ≥1000 µg per day could be reassured by the finding of normal adult levels of cortisol, and after discontinuing ICT.

References

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References
day should have a low dose short ACTH stimulation test, but the precise details of what should be done and to whom will depend on local practice and facilities.

For children who are not responding to conventional doses of ICT, and by this I think it is reasonable to imply doses up to twice the licensed doses, the clinician should address the following key questions:

**Does the child have asthma?** There has been excessive enthusiasm for the diagnosis of cough variant asthma, although ICT is superior to placebo for persistent cough in children.7 Archives has carried several papers on the difficulties parents experience in interpreting such terms as “wheeze” or “ruttles”.46 Even when convincing wheeze is present, it is not necessarily asthmatic in origin, although it usually is, and clinicians must beware of missing such diagnoses as cystic fibrosis and bronchiectasis.

Are compliance and inhaler technique satisfactory? Compliance in asthma is notoriously poor, but can be improved by suitable educational input.

Has the use of non-steroidal alternatives been fully explored? This is the point at which to consider the introduction of a long-acting β₂ agonist, montelukast, or even low-dose theophylline.

**IS IT TIME TO CONSIDER REFERRAL TO A PAEDIATRIC RESPIROLOGIST?** Finally, if high dose ICT is still considered necessary, I believe it is advisable for the time being to avoid the use of FP, which should nevertheless retain its place for use in conventional dosages.

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Inhaled corticosteroids and adrenal insufficiency

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