pregnancies fell overall, but there was a small increase in the relative difference. This potential of well intentioned programmes to increase inequalities has also been noted in the USA.¹¹

So, what lessons can we learn from these examples? It is fundamental that, as far as possible, any potential adverse effects have been considered before embarking on a new initiative. However, it is not only the effect on the population as a whole, but the potential effects, both adverse and beneficial, on the more vulnerable members of the community that have to be considered. This analysis may lead to a realisation that during the introduction of some programmes—new CHISs or changes in responsibilities—safeguards have to be put in place to ensure that the more disadvantaged do not suffer.

One of the hypotheses put forward by the Sure Start Evaluation Team to explain the worsening of some outcomes in the more disadvantaged families was that, in a more “client responsive environment”, services are used more by the relatively less disadvantaged groups, leaving fewer services available to the most disadvantaged. This has major implications for the current “choice” agenda that is being rolled out. There is a real danger: “to those that hath shall be given; from those that hath not, shall be taken”. Bearing this in mind, it is extremely important that we have a strong public health programme for children; that we monitor the overall

effect of all health and social care initiatives; and, equally importantly, their effects on the most vulnerable members of our society are closely monitored. In the current climate of the NHS, we have a duty to ensure that this is not lost in the need to cut costs and remember “the public health experience of historic patterns of the NHS, which has viewed prevention programmes as the easiest to cut and the most difficult to defend”.¹²

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Authors' affiliations

D A C Elliman, Great Ormond Street Hospital for Children, Great Ormond Street, London, UK

H Bedford, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, London, UK

Correspondence to: Dr D A C Elliman, Great Ormond Street Hospital for Children, Great Ormond Street, London WC1 3JH, UK; ellimd@gosh.nhs.uk

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Endocrinology

Very high dose inhaled corticosteroids: panacea or poison?

G Russell

Perspective on the paper by Paton *et al* (see page 808)

Only the older readers of *Archives* will remember a time when inhaled corticosteroid therapy (ICT) was not the mainstay of asthma treatment. In the 1960s asthma was an unpredictable and more or less untreatable disease, and the diagnosis was made with reluctance by doctors and accepted with dismay by parents. The therapeutic options were limited. For acute relief, isoprenaline (isoproterenol) was given by pressurised metered dose inhaler, but its effects lasted for only a few minutes, and it fell into disrepute

after only a decade, when its use appeared to be associated with increased mortality.¹ In hospital, subcutaneous adrenaline backed up by oral or intravenous corticosteroids was the mainstay of therapy. Interval management was mainly with bronchodilators such as ephedrine, theophylline, and the belladonna alkaloids, and compound preparations such as Tedral, an unlikely mixture of theophylline, ephedrine, and phenobarbital, were popular. These drugs were of undoubted benefit, but disappointingly large numbers of

children required maintenance therapy with oral corticosteroids.

The asthma clinic at the Children's Hospital in Aberdeen was established primarily to manage children who were on long term systemic corticosteroids for their asthma. My brief was to ensure that all other therapeutic possibilities were explored so as to keep the dose of corticosteroids to a minimum. Other than introducing the use of ACTH to protect growth,² I doubt if my ministrations made much difference until the arrival in rapid succession of salbutamol,³ sodium cromoglycate (cromolyn),⁴ and finally beclomethasone,⁵ which together transformed the management of asthma. As can be seen from fig 1, these new drugs rapidly made the original raison d'être of the clinic an irrelevancy, and I became a committed devotee of ICT.

INTRODUCTION OF HIGH DOSE ICT

Early experience with ICT suggested that it was more panacea than poison,⁶ and emboldened by the lack of evidence of adrenal suppression in early studies using

Figure 1 Number of patients on oral corticosteroid therapy or ACTH for three months or longer at the asthma clinic, Royal Aberdeen Children's Hospital.

conventional doses of ICT, clinicians began to use ever higher doses, a practice that started among adult physicians⁷ but was rapidly emulated by their paediatric colleagues. Although higher doses of ICT were associated fairly consistently with evidence of adrenal suppression,^{8–11} particularly when more sensitive tests such as nocturnal cortisol production¹² or the low dose ACTH test¹³ were used, the consensus view was that these biochemical findings did not translate into clinical problems, and high dose ICT became accepted practice for children with severe persistent asthma, doses of up to 800 µg per day (400 µg per day in the case of fluticasone) being sanctioned in Step 4 of the British Thoracic Society (BTS) Guidelines.¹⁴ Because of a recent change in the dose of fluticasone licensed for paediatric use, I will avoid reference to licensed doses of ICT and instead will use the terminology detailed in table 1.

BEYOND THE GUIDELINES

The BTS Guidelines included no advice on the management of those difficult cases that failed to respond to high dose ICT,^{15–16} and clinicians were left to devise their own strategies, which commonly included very high dose ICT. Remarkably little information was available to help guide such treatment. We believed that efficacy and side effects were related roughly as shown in fig 2, the precise placement of the two curves being uncertain,¹⁷ although in reality there is very little therapeutic gain to be had in moving from conventional to high dose ICT, and probably none in moving from high dose to very high dose.¹⁸ Nevertheless, the practice of

using increasingly high doses of ICT, particularly of fluticasone,¹⁹ became commonplace in the UK. It appears that better disciplined clinicians elsewhere in the world were less willing to stray beyond licensed doses, and only a tiny number of reports of adrenal failure have appeared from outside the UK.

Another factor probably encouraged the use of ever higher doses of ICT. In 2001 the manufacturers of fluticasone applied successfully to the Medicines Control Agency to have the maximum recommended dose for children increased from 200 to 400 µg per day. This undoubtedly reflected practice at the time, but left the clinician uncertain as to whether Step 4 of the Guidelines would now permit fluticasone in doses up to 800 µg per day, i.e. the same dose as for beclomethasone and budesonide which are only about half as potent.²⁰ In the event, the new Guidelines²¹ did no such thing, but whether the result of confusion or intent, very high dose fluticasone began to be used at about that time, resulting in the spate of cases of ICT related acute adrenal failure^{22–23} to which Paton *et al* have added two further cases, one fatal, in their paper.²⁴

UNANSWERED QUESTIONS

The association between high dose ICT and adrenal failure is now beyond dispute, and it is clear from Paton and colleagues' paper that significant depression of adrenal function is much more common than most of us suspected. It is equally clear that not all patients on very high doses of ICT suffer adrenal failure, and the factors that endanger or protect individual patients are unknown.

Figure 2 Relation between dose of inhaled corticosteroid, clinical efficacy, and side-effects.

Compliance with therapy is likely to be important, as is the choice of inhaler device, which has long been known to influence the intrapulmonary deposition of drugs given by metered dose inhaler. Given the known differences in metabolism between the individual compounds,^{25–26} it is hard to believe that the choice of steroid molecule is unimportant, but it will be a foolhardy clinician who decides to embark on very high dose ICT with alternative corticosteroids and to then perform a study similar to that reported by Paton *et al*. Whether adrenal failure is a class effect of all forms of ICT or is especially liable to occur on fluticasone is therefore a moot point that may never be resolved.

WHAT NEXT?

Steroid scares in the past have been of concern to clinicians because of the risk that patients might be endangered by the reduction or withdrawal of essential corticosteroid therapy.^{27–29} However, this scare is sphincter threateningly scary, as we appear to have ignored the classic dictum of *primum non nocere*, and patients are suffering serious harm and even death. If high dose ICT were a new therapy, reports of such complications would ensure that it suffered the fate of benoxaprofen or rofecoxib.

Clearly, with decades of experience of the safe and efficacious use of ICT in normal doses, changing the face of asthma as illustrated in fig 1, there can be no question of withdrawing what is probably the most useful single treatment available for asthma. However, we do need to ask ourselves if we really need very high dose ICT, and I suspect that in the majority of cases the answer will be negative.

NON-INDICATIONS FOR VERY HIGH DOSE ICT

Before discussing the use of very high dose ICT in asthma, attention must be drawn to some non-indications for its use. Cough variant asthma is a popular diagnosis in cases of otherwise unexplained cough. It is however rather rare, and the response of isolated cough to ICT is at best modest.^{30–31} This appears to have been the diagnosis in several of the

Table 1 Definitions of doses used in this paper

	Conventional dose	High dose	Very high dose
Beclomethasone and budesonide	≤ 400 µg per day	≤ 800 µg per day	> 800 µg per day
Fluticasone	≤ 200 µg per day	≤ 400 µg per day	> 400 µg per day

reported cases of ICT related adrenal failure, and while a trial of ICT may be worthwhile in children with chronic cough, there is no justification for venturing beyond conventional doses of ICT. If cough persists, rather than ratcheting up the dose of ICT, it is more likely to be profitable to look for other causes of chronic cough such as cystic fibrosis, ciliary dysmotility, or foreign body.³²

A second group of children who do not respond to ICT are those with virus associated wheeze.³³ Upper respiratory tract infection is of course a major trigger of asthmatic attacks, and paediatricians are quite reasonably anxious not to miss cases of asthma. However, children who wheeze only in the presence of infection are less likely than asthmatic children to have a personal or family history of allergies, and generally have milder wheeze³⁴ which, if it does not respond to conventional doses of ICT, would not justify high dose ICT.

USE OF VERY HIGH DOSE ICT

There are children with asthma who respond only to very high dose ICT, but such children are few and far between. One of the most worrying features of the reported cases of adrenal failure has been that clinicians sometimes appear to have persevered with increasing doses of what has obviously been unsuccessful treatment, rather than reviewing the case to ensure that the diagnosis is correct, that avoidable triggers have been identified and avoided, that compliance with treatment is satisfactory, and that the use of non-steroidal medication is maximised using a non-steroidal therapeutic armamentarium vastly more effective than anything available to us in the 1960s.

In deciding to use very high dose ICT, following Paton and colleagues' paper, a new balance of advantage must be struck. In managing "ordinary" cases of asthma with conventional doses of ICT, the objective is to abolish or minimise the impact of the disease, secure in the knowledge that systemic side-effects will be minimal. But when very high dose ICT is contemplated, the impact of the disease must be balanced against the known risk posed by this treatment, and such treatment should clearly be reserved for children whose disease in not only unresponsive to conventional or high dose ICT, but is also severe enough to justify potentially very dangerous treatment. Such cases will be unusual, and should certainly be under the care of a paediatric respirologist and, I would suggest, a paediatric endocrinologist. As Visser and colleagues³⁵ put it, very high doses of fluticasone propionate should only be prescribed in exceptions.

For those exceptional patients who genuinely appear to respond only to very high dose ICT, and whose dose cannot be stepped down successfully, we must do everything possible to ensure their safety. Such patients should be kept under close review to ensure compliance with treatment, and monitored regularly for adverse effects. It is no longer enough to rely on a normal growth pattern to exclude systemic effects of ICT—a notable feature of the children with adrenal failure has been how many of them were growing normally. I can see no option but to perform regular endocrine assessments on all of them—after all, we check liver function on all patients on valproate, looking for a complication much rarer than adrenal failure following high dose ICT.

However, the best solution of all would be to avoid using very high dose ICT in the first place.

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Correspondence to: Dr G Russell, Department of Child Health, University of Aberdeen, Royal Aberdeen Children's Hospital, Aberdeen AB25 2ZG, UK; libra@ifb.co.uk

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