

# Inhaled corticosteroids: benefits and risks

Inhaled corticosteroids are an established treatment for asthma. Their success is based on their ability to improve control of asthma, to allow the reduction of other drugs, such as oral corticosteroids, and perhaps to limit the risk of long term decline in lung function. These impressive advantages are achieved with a few common unwanted effects, such as oral candidiasis and dysphonia, which are relatively trivial, more serious side effects occurring only towards the top of the recommended dose range.

Not surprisingly, this good risk: benefit record has led to a steadily growing number of prescriptions, but also to carelessness in doctors' attitudes. Inhaled corticosteroids are usually prescribed by number of puffs rather than actual dose and are often spoken of as "high dose" or "low dose" in a way that does not occur with other medication.

Systemic side effects do undoubtedly occur at doses above 1 mg/day but these may be an acceptable risk in a patient who would otherwise have to take oral corticosteroids. Precise knowledge of the true benefits and risks of inhaled corticosteroids at different doses is hard to come by and dose-response curves for wanted and unwanted effects are not well established. The aim of this article is to review the published evidence relating the dose of inhaled corticosteroids to benefits and risks, both to aid rational prescribing and to draw attention to the rather large gaps in our knowledge.

## Benefits

The benefits of inhaled corticosteroids were first suggested by their basic pharmacological properties and then established by clinical trials. These trials were originally designed to find out whether inhaled corticosteroids could replace oral corticosteroids. Nowadays inhaled corticosteroids are usually started as the first form of steroid treatment and so the early trials are not as relevant as they were and fail to answer many of today's questions.

## PHARMACOLOGY

The most important properties of all inhaled corticosteroids are high topical potency, usually established in animal models of uncertain relevance to human asthma, combined with low systemic bioavailability.<sup>1</sup> On these grounds alone beclomethasone dipropionate and budesonide show major advantages over oral corticosteroids such as prednisolone, and theory has been borne out in clinical practice. The pharmacological properties of the different inhaled corticosteroids can be compared and advantages tentatively deduced. Any such advantages, before they are accepted, need to be confirmed by clinical trials. For example, budesonide, as judged by the vasoconstrictor test,<sup>2</sup> is a more potent anti-inflammatory drug than beclomethasone dipropionate but seems no more effective in clinical trials in asthma (see below). The theoretical advantages of the next generation of inhaled corticosteroids will need to be evaluated critically in the same way. Similarly, such animal studies cannot be used to predict a dose-response curve for inhaled corticosteroids in asthma and for this purpose only clinical trials will do.

## CLINICAL TRIALS

Clinical trials come in two sizes: short term studies with a good prospective design and longer studies, which often have design faults but are much closer to real life. The key conclusions from both of these types of study are that

inhaled corticosteroids improve asthma control and allow reduction or withdrawal of systemic steroid treatment, but dose-response data are scanty.

Some short term studies show increasing benefit with increasing dose but many do not (table 1). Long term studies are fewer and more difficult to assess but in general show better responses with higher doses, albeit in highly selected patients. The pioneer study was the Brompton Medical Research Council trial.<sup>9</sup> This compared doses of 400 and 800 µg/day in two ways. For the first 28 weeks parallel groups of patients with asthma were compared and the larger dose was found to allow a greater reduction in oral corticosteroids. For the second 28 weeks those who had failed to halve their oral steroids on 400 µg/day took twice the dose. Surprisingly, no additional benefit ensued. There are only two other long term studies, which are open, uncontrolled, retrospective surveys of clinical practice. Toogood *et al* reported the response to inhaled corticosteroids in a group of patients with severe asthma requiring an average of 12 mg/day of prednisolone.<sup>10</sup> Beclomethasone dipropionate was progressively increased from 0.2 to 1.6 mg/day while the prednisolone dose was held stable. The results suggest better lung function and asthma control with increasing dose of inhaled corticosteroids and show no plateau on the dose-response curve. An important additional finding was that the dose-response curves were different for different measures of response—for example, flow rates do not respond in the same way as disability. Smith and Hodson<sup>11</sup> reported experience with the "high dose" beclomethasone dipropionate inhaler (250 µg/puff) in 293 patients whose dose had been increased either because of poor asthma control or because of the continuing need to take oral corticosteroids. This allowed a comparison between "standard" (400 µg/day) and "high" doses (500–2000 µg/day) and showed a benefit from the latter, though most of the "high dose" patients took only 1000 µg/day. Recently, in an open trial, nebulised budesonide 4–8 mg/day allowed 14 patients who had taken at least 7.5 mg/day of prednisolone for two years or more to stop and also resulted in slight improvement in asthma control.<sup>12</sup> Part of the benefit of such high doses may be systemic steroid replacement in patients with adrenal suppression from long term steroids.

Two studies have compared inhaled with oral corticosteroids in relatively small groups of patients. In the first study patients taking regular oral steroids were asked to

Table 1 Studies of the dose-response characteristics of inhaled beclomethasone dipropionate (BDP) and budesonide (BUD)

First author	n	Drug	Doses (µg/day)	Dose-response effect?
<i>Short term studies</i>				
Gaddie <sup>3</sup>	15	BDP	400–1600	No
Costello <sup>4</sup>	5	BDP	400–1000	Yes
Boe <sup>5</sup>	128	BDP BUD	400–1000	No
Bjorkander <sup>6</sup>	17	BDP	200–400	No
Toogood <sup>7</sup>	34	BUD	400–3200	Yes (no plateau)
Johansson <sup>8</sup>	18	BUD	100–1600	Yes (up to 400 µg/day)
<i>Long term studies</i>				
Brompton-MRC <sup>9</sup>	95	BDP	400–800	Yes and no
Toogood <sup>10</sup>	34	BDP	200–1600	Yes
Smith <sup>11</sup>	293	BDP	400–1600	Yes (data adequate to 1000 µg/day)

take supplementary steroids in various ways. The authors suggested that budesonide 400  $\mu$ g/day was equivalent to prednisolone 10 mg/day but failed to show any convincing dose-response effect.<sup>13</sup> In the second study Toogood *et al* investigated four doses of budesonide and six of prednisolone and provided some evidence of a dose-response effect up to at least 3.2 mg/day of budesonide.<sup>7</sup> This study showed unequivocal systemic effects at high doses. Again there were different response curves for different outcomes.

#### COMPARISONS BETWEEN BECLOMETHASONE DIPROPIONATE AND BUDESONIDE

At least 17 clinical trials have compared beclomethasone dipropionate and budesonide in asthma.<sup>14-27</sup> Most have found no important differences. The few small advantages are likely to be due to chance as a formidable number of comparisons were made. In contrast, comparisons between these two drugs in allergic rhinitis have tended to favour budesonide.<sup>28,29</sup>

There are, of course, several reasons why comparisons between two drugs or two doses of a single inhaled steroid might fail to show a difference: (1) the doses may have been too high—that is, both may have been on the plateau of the dose-response curve; (2) the asthma may have been too stable during the trial period and so no dose changes could have made any difference; (3) too few patients might have been studied to allow any conclusion; and, finally, the finding of no difference might be real.

#### Risks

Risks are extremely low and in particular there are no reports of any life threatening events. Minor adverse effects certainly occur but the main focus of the debate is on the clinical relevance of the systemic changes that can be detected when inhaled corticosteroids are used in higher doses for short periods.

#### SYSTEMIC CHANGES

Systemic changes can be summarised as changes in blood cells, general metabolism, the hypothalamic-pituitary-adrenal axis, and bone metabolism; most attention has focussed on the last two. Inhaled corticosteroids cause a fall in blood lymphocyte and eosinophil counts with a rise in the neutrophil count and in the blood sugar concentration.<sup>1</sup> These changes are detected with 500  $\mu$ g in healthy volunteers and increase with dose. They probably have no clinical importance, but have not been systematically studied in patients who are old or have diabetes or liver disease. Similarly, minor changes occur in blood concentrations of insulin, cholesterol, lactate, pyruvate, and glycerol in normal subjects taking 1000  $\mu$ g/day of beclomethasone dipropionate.<sup>30</sup> These have not been studied in patients with asthma.

#### Hypothalamic-pituitary-adrenal axis

Most studies of the effects on the hypothalamic-pituitary-adrenal axis have examined morning cortisol,<sup>2,16,22,27</sup> a relatively crude measure; many have included the synacthen response,<sup>6,15,26,31,33,34</sup> which is better, or 24 hour urinary free cortisol excretion, which is better still,<sup>24,28,32,35,38,39</sup> and only one has assessed full axis function on the basis of insulin hypoglycaemia.<sup>35</sup> All the authors agree that no significant changes occur at doses below 800  $\mu$ g/day in either adults or children, and that with higher doses abnormalities become more common. There is no clearcut threshold for suppression of the hypothalamic-pituitary-adrenal axis but the evidence is difficult to interpret because most patients have previously taken oral corticosteroids and because different delivery systems are used. Brown *et*

*al*<sup>35</sup> detected abnormalities in 16 of 78 patients taking 1.2–2.65 mg/day.

The clinical relevance of these changes is not known. Brown *et al*<sup>35</sup> recommend that screening tests of hypothalamic-pituitary-adrenal axis function should be performed in all patients taking more than 1.5 mg/day but do not indicate when or how often. They also state that such patients should carry a steroid card unless hypothalamic-pituitary-adrenal axis function has been shown to be normal. This advice may be misleading as it ignores the uncertainties about the relative values of the different screening tests. In a companion paper the same authors show that measurement of 24 hour urinary free cortisol excretion is as good as the synacthen test.<sup>36</sup> They did not, however, do routine insulin hypoglycaemia tests and so we do not know how many patients with suppression of the hypothalamic-pituitary-adrenal axis these more simple screens would miss. This could be important as abnormalities in the cortisol response to insulin hypoglycaemia are surprisingly common in patients taking low doses of oral corticosteroids for short periods.<sup>37</sup>

Beclomethasone dipropionate and budesonide have been compared for their effects on the hypothalamic-pituitary-adrenal axis in at least 16 studies. No differences between the two drugs have been found in adults, though often different doses or delivery systems, or both, have been used. In contrast, minor differences favouring budesonide have been found in children. Bisgaard<sup>38</sup> showed that urinary free cortisol excretion fell when beclomethasone dipropionate dose rose from 200 to 800  $\mu$ g/day, whereas this did not apply to budesonide. Pedersen<sup>39</sup> showed that urinary free cortisol excretion was unequivocally higher in children taking budesonide than in those taking beclomethasone dipropionate. In both of these studies, however, the differences were small and of doubtful clinical importance.

#### Bone metabolism

There is suggestive evidence that inhaled corticosteroids can play a part in the development of osteoporosis. This evidence comes both from short term studies of bone metabolism in normal subjects (table 2) and from bone density measurements in patients with asthma (table 3). The short term studies can be criticised as they only predict that osteoporosis is likely to occur with long term use but do not prove that it actually does. The studies in asthmatic patients can be criticised as oral corticosteroids has always been taken previously and so may be, at least in part, responsible for the changes; such a study, by Packe *et al*,<sup>53</sup> is reported in this issue of *Thorax* (p415). Furthermore, the relation between low bone density and clinical events is uncertain and so the true importance of the reported changes is still not known. Nevertheless, the fact that changes can be detected with 400  $\mu$ g/day and increase with dose strongly suggests that clinical problems will occur in

Table 2 Effect of inhaled beclomethasone dipropionate (BDP) and budesonide (BUD) on bone metabolism in normal volunteers

Authors	n	Drug ( $\mu$ g/day)	Results
Ali <sup>40</sup>	12	BDP 2000	Serum alkaline phosphatase↓ Urine hydroxyproline: creatinine ratio↓ No changes
		BUD 1800	
Jennings <sup>52</sup>	12	BUD 800–3200	Osteocalcin↓ at 3200 $\mu$ g/day
Meeran <sup>50</sup>	30	BDP 1000	Osteocalcin↓
Peretz <sup>49</sup>	10	BDP 1000	No detectable changes
Pouw <sup>41</sup>	8	BDP 2000	Osteocalcin↓
Teelucksingh <sup>42</sup>	16	BDP 400–2000	Osteocalcin↓
Toogood <sup>43</sup>		BUD 600–2400	No detectable changes

**Table 3** Bone mass or density and osteocalcin in patients taking inhaled corticosteroids for asthma\*

Author	n	Measurement	Result
Konig <sup>46</sup>	18	Bone density	No change
		Osteocalcin	No change
Luengo <sup>47</sup>	21	Bone mass	No change
Packe <sup>33</sup>	20	Bone density	20% reduction
Poulijoko <sup>31</sup>	9	Osteocalcin	Reduced
Reid <sup>44</sup>	22	Total body calcium	8.8% reduction
Stead <sup>45</sup>	11	Bone density	Reduced
Wolff <sup>46</sup>	5	Bone density	No change

\*Most had also had short courses of oral steroids for exacerbations.

patients treated with high doses of inhaled corticosteroids for long periods. Although this may well be an acceptable hazard for the minority of patients with severe asthma, the majority with mild asthma should not be exposed to the risk. The additional finding that budesonide may have less effect on bone metabolism than beclomethasone dipropionate is in line with the drug's slightly more favourable topical-systemic efficacy profile, but it has not yet been confirmed by comparative studies of bone density.

#### Other systemic side effects

**Cataracts**<sup>54-59</sup> Although some reports have suggested a link between inhaled corticosteroids and cataract formation, none have clearly proved that such an associated exists. Certainly some patients have developed cataracts while taking inhaled corticosteroids but the combination of previous oral steroids and age is likely to have been at least in part responsible. Posterior subcapsular cataracts occur in about 1% of normal people aged 50-60 and much more evidence is needed before inhaled corticosteroids can be blamed. Nevertheless, systemic absorption of inhaled steroids increases with dose and this is likely to assist cataract formation.

**Skin thinning and bruising**<sup>60-61</sup> Purpura and dermal thinning also occur in patients taking inhaled corticosteroids and there is a dose-response effect. Capewell *et al*<sup>29</sup> reported frequencies of purpura in a clinic population as follows: controls 12%, beclomethasone dipropionate 400 µg/day 33%, beclomethasone dipropionate 2000 µg/day 48%. Dermal thickness was normal in those taking 400 µg/day group but reduced with 2000 µg/day. The importance of this report is not only that patients are experiencing an unpleasant side effect but also that it shows a clearcut systemic side effect that starts in the low dose range and increases with dose.

**Mania**<sup>62</sup> Two cases of mania have been reported in association with a beclomethasone dipropionate nasal spray, which was probably the cause. A handful of other reports have mentioned depression, euphoria, insomnia, nightmares, and somnolence in patients taking beclomethasone dipropionate for asthma. Such complaints are so common that beclomethasone dipropionate cannot be established as the cause, but systemic absorption may be a contributory factor in predisposed individuals.

**Slowing of growth**<sup>63-70</sup> Growth may be slowed down by undertreated asthma and by systemic corticosteroids. It has therefore been difficult to determine whether inhaled corticosteroids have an independent effect on children's growth rates. Some studies of inhaled steroids in doses of 400 µg/day or less have shown no change in growth rate. In contrast, inhaled steroids in higher doses have sometimes

been associated with growth impairment. Some studies have shown a growth spurt after the start of treatment with inhaled steroids, presumed to be due to an improvement in asthma control. Again, systemic absorption will obviously slow growth if the dose is high enough but it is not clear at which dose this will become inevitable. A dose of 200-400 µg/day is most unlikely to affect growth and higher doses are seldom needed for asthma control.

The data are inadequate for comparing beclomethasone dipropionate and budesonide for any of these adverse effects.

#### Topical changes

**Dysphonia** Some change in the quality of the voice is quite common with inhaled corticosteroids and usually does not matter.<sup>71 72</sup> It can, however be a disabling side effect for singers and others who live by their voice. The effect is dose related and can be minimised by using spacer devices and techniques that limit oropharyngeal deposition of the drug. Slow inhalation, use of a spacer device, and gargling all limit the dysphonia.

**Candidiasis** Positive throat swabs are common in the normal population (20-30%) and as frequent as 40% in patients taking inhaled corticosteroids. Symptomatic candidiasis, however, affects less than 5% and can usually be controlled by a combination of measures to limit oropharyngeal deposition and, in some cases, topical antifungal treatment.<sup>73 74</sup>

#### Conclusions

- 1 Dose-response studies of inhaled corticosteroids in asthma give conflicting results. (a) Many patients have no benefit from an increase in dose above 400 µg/day. (b) A minority of patients with severe asthma benefit from an increase in dose above 800 µg/day. (c) The plateau on the dose-response curve differs from patient to patient and according to which response is studied; no universal maximum effective dose can be defined.
- 2 Systemic absorption occurs and produces detectable effects even at low doses.
- 3 Clinically important adverse effects are rare with doses of 800 µg/day or less.
- 4 Adverse effects occur above 800 µg/day and are related to dose. Long term use of doses greater than 800 µg/day is likely to contribute to osteoporosis.
- 5 Comparisons between beclomethasone dipropionate and budesonide show (a) no significant differences in asthma control and (b) some differences in the effects of systemic absorption in favour of budesonide.

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