PAPERS AND SHORT REPORTS

Combined oral and nasal beclomethasone dipropionate in children with atopic eczema: a randomised controlled trial

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Abstract

In a double blind, placebo controlled, crossover trial in 26 children with severe atopic eczema those receiving four weeks' treatment with combined oral plus nasal beclomethasone dipropionate improved significantly more than those receiving placebo. No adverse effects were observed, but 24 hour urinary cortisol excretion was slightly reduced.

This combination may provide effective treatment in refractory atopic eczema with relatively little of the danger associated with systemic administration of prednisolone and other traditional corticosteroids.

Introduction

Atopic eczema is a common disorder in children in the United Kingdom. In most cases it is mild and can be adequately controlled by emollients and weak topical corticosteroids. There are, however, many children in whom the disease is severe and disabling. In these children simple therapeutic measures often fail, and systemic corticosteroid administration may be considered. Because of the well known hazards of traditional systemic corticosteroids such as prednisolone, however, there is a great need for a safer alternative treatment. The unpublished observation of Dr G M Cochrane that high dose beclomethasone dipropionate given by inhalation to children with asthma

apparently helped coexisting atopic eczema encouraged us to try the drug in refractory atopic eczema alone.

Beclomethasone dipropionate is a synthetic corticosteroid with potent anti-inflammatory properties¹ and is effective when given locally for asthma and allergic rhinitis.²⁻⁴ Most of an inhaled dose is swallowed,⁵ and much of this is systemically absorbed.¹⁻⁶ The proportion of a nasal dose that is absorbed is probably less than that of an equivalent bronchial dose.⁷ After absorption beclomethasone dipropionate is rapidly metabolised in the liver to inactive metabolites.¹⁻⁶ The long term use of beclomethasone dipropionate in asthma and allergic rhinitis has been associated with remarkably few adverse effects, either local or systemic,⁸⁻¹¹ and the growth of children receiving long term treatment for asthma is normal.⁹⁻¹¹

As inhaled beclomethasone dipropionate is largely swallowed, we performed an open pilot study in which we gave beclomethasone dipropionate by mouth to children with atopic eczema resistant to standard treatment. This appeared to be beneficial, and treatment combined with inhaled beclomethasone dipropionate was apparently more effective than oral or nasal beclomethasone dipropionate alone, so we embarked on the controlled trial of combined treatment which is the subject of this report.

Patients and methods

Twenty seven children (14 boys, 13 girls, aged 3-14 years, mean 6.5 years) entered the study. All had had moderate or severe atopic eczema for at least three months which had failed to respond adequately to conventional therapy with emollients, weak topical corticosteroids, and systemic antihistamines. None were receiving systemic or inhaled corticosteroids.

The trial was double blind and placebo controlled with crossover. The order of administration of treatments was allocated by random numbers. The treatment comprised oral plus nasal beclomethasone dipropionate given four times daily for four weeks. Each oral dose was the contents of a 200 µg Becotide Rotacap suspended in about 20 ml of water; each nasal dose was given as a single metered dose (50 µg) from a Beconase aerosol via each nostril (total daily dose 1200 µg beclomethasone dipropionate). Rotacaps plus a nasal aerosol, both of identical appearance but containing only carrier and propellant respectively, were used during the placebo period. There was a four week washout period between the two treatment periods.

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Parents were asked to continue their child's usual topical treatments and oral antihistamine throughout the trial but to use them only when needed. Twenty four of the children were using a topical corticosteroid, either 1% hydrocortisone or 0.1% hydrocortisone 17-butyrate ointment. Most were taking a single nightly dose of trimeprazine tartrate syrup. Some children had been on empirical elimination diets for at least six weeks before entry to the trial; these were continued unchanged throughout the trial.

Evaluations were made at the beginning and end of each treatment period. The skin surface was divided into 20 separate zones of roughly equal area. A score (0-3) was recorded for each zone for (a) redness, (b) surface damage (vesiculation, crusting, or excoriation, or any combination of them), and (c) lichenification. These scores were added to give a total score of 0-60 for each feature. The extent of disease was estimated by counting the number of zones in which any of the above features were observed. Scores at the beginning of each treatment period were subtracted from those at the end, so the differences were positive if the eczema had worsened and negative if it had improved.

Parents used a visual analogue scale to record scores (0-10) for daytime itch and night time sleep disturbance due to itch for each 24 hour period. They also recorded on a diary card the daily dose of antihistamine and topical corticosteroid (measured in inches expressed from the tube). Because different oral antihistamines and topical corticosteroids were used by the children the amounts used daily during the active treatment period were expressed as a ratio of those used daily during the placebo period. For those patients who used these treatments during one treatment period but not during the other, the values 1 and 0 were assigned respectively for the mean daily dose. Diary card scores for the first week of each treatment period were discarded, to minimise carry over effects.

At the end of each treatment period parents assessed the change in both severity of the eczema and general well being on the scale: -2=very much better; -1=somewhat better; 0=no change; +1=somewhat worse; and +2=very much worse. At the end of the study parents were asked to state any preference for either treatment period.

The patients were prick tested with extracts (Bencard) of Timothy grass pollen, *Dermatophagoides pteronyssinus*, cat dander, *Aspergillus fumigatus*, whole egg, whole cows' milk, and a negative control. IgE antibodies to Timothy grass pollen, *D. pteronyssinus*, cat dander, whole egg, and whole cows' milk were measured by the radio-allergosorbent method, using sera diluted 1/10 and 1/25; results were regarded as positive if counts bound were 10 times those of human cord blood. Total serum IgE was measured by a double antibody radio-immunoassay.

The 24 hour urinary excretion of free cortisol was determined during the last week of each treatment period with the Amerlex cortisol radioimmunoassay kit. Urinary creatinine excretion was also determined.

The therapeutic effects and order effects were compared using the two tailed Wilcoxon's matched pairs non-parametric test. Treatment-order interactions were sought by comparing the total response (response to active treatment plus response to placebo treatment) in those given placebo first with that in those given the active treatment first.

We used the Wilcoxon's test for unpaired data for this and for the comparisons between responses in boys and girls. Product moment correlation coefficients were calculated—for example, for the relationship between response and serum IgE concentrations.

This study was approved by the hospital's standing committee on ethical practice. Exemption from the need to obtain a clinical trial licence was provided by the Committee on Safety of Medicines. Written informed consent was obtained from parents, who were provided with a drug information card.

FIG 1—Improvement in surface damage scores during treatment with oral plus nasal beclomethasone dipropionate or placebo. Lines join scores for individual subjects.

Results

Twenty six children completed the study; one child, who developed whooping cough, withdrew. Seventeen had a history of recurrent wheeze and 14 a history of recurrent rhinitis or cutaneous wealing, or both. All the 24 subjects tested developed immediate weals of at least 2 mm diameter to one or more of the six prick test extracts and had IgE antibody to at least one allergen and a raised total serum IgE (mean: 3900 IU/ml, range: 380-8000 IU/ml; upper limit of normal:

TABLE I—Clinician's assessments: treatment and order effects

	Maximum possible score	Mean score on entry	Mean change during:		Period 1 v period 2 (p)	Mean change during:		Beclomethasone dipropionate v placebo (p)
			Period 1	Period 2		Beclomethasone dipropionate	Placebo	
Redness	60	25	-2.2	-5.1	>0.10	-6.3	-1.0	<0.02
Surface damage	60	26	-2.5	-3.3	>0.10	-6.5	+0.7	<0.01
Lichenification	60	19	-2.0	0.0	>0.10	-2.7	+0.7	<0.01
No of zones affected—that is, showing any of the above	20	19	+0.1	-0.5	>0.10	-0.7	+0.3	<0.02

TABLE II—Diary scores: treatment and order effects

	Maximum possible score	Mean score during:		Period 1 v period 2 (p)	Mean score during:		Beclomethasone dipropionate v placebo (p)
		Period 1	Period 2		Beclomethasone dipropionate	Placebo	
Daytime itch	10	3.5	2.7	<0.02	2.8	3.5	<0.05
Sleep loss	10	2.7	1.9	<0.01	2.2	2.4	>0.10
Daily dose of antihistamines (inches)		0.84	0.82	>0.10	0.71	0.95	<0.05
Daily dose of topical corticosteroids (inches)		1.02	0.82	<0.05	0.99	0.95	>0.10

150 IU/ml). The two subjects who declined prick testing and venepuncture had recurrent wheeze and either rhinitis or urticaria.

All the children had extensive eczema, with a mean of 19 of the 20 zones affected. The three assessments of severity and the assessment of extent all showed significantly greater improvements on beclomethasone dipropionate than on placebo (table I). The most consistent effect was on surface damage (fig 1), the feature most capable of quick change. There were no significant order effects (table I) or treatment-order interactions.

The change in scores during treatment with beclomethasone dipropionate did not differ significantly between boys and girls or between children with or without other atopic diseases. There was no significant correlation between the response to beclomethasone dipropionate and severity of disease on entry or total serum IgE. There was, however, a significant correlation between favourable responses and a positive serum IgE antibody to hens' egg ($r=0.51$; $df=22$; $p<0.02$). A similar trend, not statistically significant, was seen in prick tests to whole eggs.

Parental scores for daytime itch and antihistamine use were significantly lower on beclomethasone dipropionate than on placebo (table II), but neither the use of topical corticosteroids nor sleep disturbance showed significant changes. Significant order effects were seen for all variables except antihistamine use, but no significant treatment-order interactions were detected.

The parents' overall assessment of eczema activity was significantly lower on beclomethasone dipropionate (mean score -0.8 for beclomethasone dipropionate and -0.2 for placebo ($p<0.05$), but there was a significant treatment-order interaction ($p<0.05$), with greater relative benefit from beclomethasone dipropionate and reduced benefit from placebo in the second period. Of the 17 parents who expressed a final preference, 12 preferred beclomethasone dipropionate and five preferred placebo ($p=0.29$).

Of 52 urine specimens, three from two subjects were rejected because the creatinine content was less than predicted. Twenty four hour urinary free cortisol excretion was lower after four weeks of treatment with beclomethasone dipropionate than after placebo treatment in all but two children (fig 2), ($p<0.01$). There was no

FIG 2—Urinary cortisol excretion (per 24 hours) in patients after four weeks of oral plus nasal beclomethasone dipropionate or placebo. Lines join scores for individual subjects; results are shown according to order of treatments. The horizontal broken lines show the 95% confidence limits for values obtained during placebo administration, using log transformed data.

significant difference in 24 hour urinary free cortisol excretion during placebo treatment between those subjects treated with beclomethasone dipropionate in the first period and those treated in the second, implying that the suppressive effect lasted for less than eight weeks after stopping beclomethasone dipropionate. Reduction in surface damage, the feature showing the greatest benefit from beclomethasone dipropionate, did not correlate significantly with either the degree of cortisol suppression or the patient's age.

Symptomatic adverse effects were reported during neither beclomethasone dipropionate nor placebo therapy. Skin infections occurred in three children during treatment with beclomethasone dipropionate and five during placebo therapy.

Discussion

This trial showed a beneficial effect on atopic eczema of the combination of orally and nasally administered beclomethasone dipropionate. By the most discriminating criterion, surface damage, about half the children showed a very much better response to beclomethasone dipropionate than to placebo. The clinical usefulness of this effect is suggested by the parallel reduction in itch and decreased use of antihistamines. Perhaps surprisingly, topical corticosteroid use was no less on beclomethasone dipropionate, but this may have been because many parents apply such preparations as much for their emollient properties as for any anti-inflammatory effect.

A fall in urinary cortisol excretion during treatment with beclomethasone dipropionate has been previously reported¹² and shows that the drug does have some systemic effect, thus raising anxiety about its long term safety at these doses in children. Nevertheless, only three of the values obtained during treatment with beclomethasone dipropionate fell below the 95% confidence limits for values obtained during placebo administration; the degree of adrenal suppression was therefore relatively small after four weeks' treatment. Despite this concern, experience in asthmatic children has been very favourable even though inhaled beclomethasone dipropionate has a greater adrenal suppressive effect than oral beclomethasone dipropionate,¹³ presumably because it is subject to less rapid hepatic metabolism. Asthmatic children grow normally when inhaling around 400 µg of beclomethasone dipropionate daily for several years,⁹⁻¹¹ though normal growth has not yet been established for the higher doses given in our study. It is, however, reassuring that no significant impairment in the results of serial tetracosactrin tests could be shown in adults on long term therapy with inhaled beclomethasone dipropionate in doses up to 2000 µg daily.¹⁴ We plan to study adrenal and pituitary function and growth in our patients at yearly intervals and investigate the possibility that lower doses might be effective.

We do not know how beclomethasone dipropionate improves atopic eczema. The adrenal suppression is evidence of a systemic effect, so the therapeutic effect may also be systemically mediated. The benefits of treatment with beclomethasone dipropionate seem, however, disproportionate to the degree of adrenal suppression when compared with the virtually total suppression of endogenous cortisol secretion observed in children gaining comparable benefit from systemic corticosteroids such as prednisolone. Beclomethasone dipropionate might work quite differently, by a local effect. Many patients with atopic eczema appear to have increased gastrointestinal permeability to antigens and to inert macromolecules such as lactulose and polyethylene glycol,¹⁵⁻¹⁷ possibly because of local allergic reactions in the gut. Beclomethasone dipropionate might reduce mucosal antigen permeability or prevent the release of inflammatory mediators from the sites of mucosal allergic reactions, or both, in the gastrointestinal tract and possibly also in the nose, though the requirement for concurrent nasal therapy remains to be established.

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Acute cholecystitis and thiazides

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Abstract

Drugs purchased by a random sample (17 000) of the population of Jämtland county, Sweden, are continuously monitored. Patients who had been admitted to the county's only hospital with acute cholecystitis and who were part of this sample were studied, and controls matched for age and sex were drawn from the sample. The purchase of thiazides and other drugs prescribed to the patients with acute cholecystitis was compared with that of the controls. The estimated relative risk of developing acute cholecystitis in patients who had purchased thiazides in the year before admission to hospital, as compared with those who had not, was 2.1 (95% confidence limit 1.1-3.9).

As it has been reliably reported that the use of thiazides is not itself associated with cholelithiasis, the association found between thiazides and cholecystitis suggests that thiazides may increase the risk of acute cholecystitis developing in a patient with gall stones.

Introduction

Case-control studies of lifetime drug histories have provided evidence both for and against the view that use of thiazides is associated with cholecystitis.^{1,2} We were able to take a different approach by taking advantage of the continuous recording of all purchases of drugs prescribed to a random sample of the population of the county served by our hospital, and of the fact that residents of the county with acute cholecystitis are treated only at this hospital.

Patients and methods

From 1 April 1974 to 31 August 1983, 728 patients were treated at Östersunds Sjukhus, the only hospital in the county, for acute cholecystitis. The regulations of the Swedish health service do not permit residents of one county to be admitted to hospitals outside that county

unless they fall ill elsewhere. As we have a policy of performing early cholecystectomy the diagnosis was confirmed at operation in most cases.³ In the few patients in whom this was not so all the symptoms and signs of acute cholecystitis had been present but the gall bladder was not visualised at cholecystography or cholescintigraphy, or ultrasonography indicated the presence of gall stones.

Since 1970 a record has been kept of all prescribed drugs dispensed to a sample of residents of the county. This sample, selected on the basis of date of birth, constitutes 13% of the entire population of the county.⁴ The subjects are identified by number and their records arranged according to date of birth. Pharmacies record and file on computer all prescriptions dispensed to these subjects.⁵

During the period under study 91 patients admitted to hospital with acute cholecystitis also formed part of the random sample whose purchase of drugs was being monitored. Forty four were men and 47 women, and their median age was 65. For each of these 91 patients the next four subjects of the same sex were taken from the random sample and served as controls. As the subjects in the random sample are arranged according to date of birth the controls were closely matched for age. These controls had not been treated for acute cholecystitis during the period under study. A review was conducted of drugs purchased either recently or in the past by the 91 patients and the 364 controls. Recent purchase was defined as the purchase of a prescribed drug within one year of the patient's admission to hospital. Past purchase was defined as the purchase of a drug one to five years before the patient's admission to hospital. Patients and controls were compared for their recent and past purchase of thiazides, non-thiazide diuretics, nitrofurantoin, steroid ointment, and nitrazepam. The case histories of the 91 patients with acute cholecystitis were reviewed, and the clinical, radiological, and operative findings in those who had purchased thiazides before admission were compared with the findings in those who had not. Relative risks and 95% confidence limits were calculated.⁶

Results

The table shows how many of the 91 patients with acute cholecystitis and the 364 controls had purchased thiazides recently, in the past, or not at all and gives the relative risk and 95% confidence limits for each group. The relative risk for recent purchase was 2.1 (95% confidence interval 1.1-3.9). A further subdivision based on the number of years over which purchase had taken place showed that the relative risk increased with time, but this was not analysed statistically as the numbers were small. No significant association was found between past purchase and acute cholecystitis (table).

The records showed that non-thiazide diuretics had been purchased recently by seven of the patients with acute cholecystitis and 30 of the controls. The estimated relative risk was 0.9 (95% confidence limits 0.4-2.1). Past purchase of non-thiazide diuretics had been recorded in only two patients and 17 controls, giving a relative risk estimate of 0.5 with a 95% confidence interval including unity. The proportion of patients with acute cholecystitis who had made recent purchases of

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