

Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study

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Abstract

Objective To explore the efficacy and safety of fluticasone propionate, cream and ointment, applied twice weekly in addition to maintenance treatment with emollients, in reducing the risk of relapse of chronic recurrent atopic dermatitis.

Design Randomised, double blind, parallel group study of 20 weeks' duration.

Setting Dermatology outpatient clinics (6 countries, 39 centres).

Participants Adult (aged 12-65) patients with moderate to severe atopic dermatitis who were experiencing a flare.

Methods Participants applied fluticasone propionate (0.05% cream or 0.005% ointment; once or twice daily) regularly for four weeks to stabilise their condition. The patients whose disease was brought under control then continued into a 16 week maintenance phase, applying emollient on a daily basis with a bath oil as needed and either the same formulation of fluticasone propionate or its placebo base (emollient alone) twice weekly to the areas that were usually affected.

Main outcome measure Time to relapse of atopic dermatitis during maintenance phase.

Results 376 patients entered the stabilisation phase, and 295 continued into the maintenance phase. After 16 weeks in the maintenance phase, the disease remained under control in 133 patients (87 using fluticasone propionate twice weekly, 46 using emollient alone), 135 (40 fluticasone propionate, 95 emollient) had experienced a relapse, and 27 had discontinued. Median time to relapse was six weeks for emollient alone compared with more than 16 weeks for additional fluticasone propionate. Patients who applied fluticasone propionate cream twice weekly were 5.8 times less likely (95% confidence interval 3.1 to 10.8, $P < 0.001$) and patients using fluticasone propionate ointment 1.9 times less likely (1.2 to 3.2, $P = 0.010$) to have a relapse than patients applying emollient alone. The groups showed no differences in adverse events.

Conclusion After atopic dermatitis had been stabilised the addition of fluticasone propionate twice

weekly to maintenance treatment with emollients significantly reduced the risk of relapse.

Introduction

Most practitioners use one of two approaches for the long term treatment of moderate to severe atopic dermatitis: either a potent topical corticosteroid followed by a lower potency preparation as the condition improves or a short course of topical corticosteroid followed by a maintenance regimen of emollients.¹ Yet there is little evidence to support either practice.¹⁻² Others have suggested a maintenance treatment of emollient combined with intermittent topical corticosteroid.³ This approach was investigated recently in a small study, which showed that remission of atopic dermatitis can be maintained with daily emollient plus fluticasone propionate applied twice weekly to areas of the skin that had healed but were prone to relapse.⁴

In the United Kingdom both the ointment and the cream formulations of fluticasone propionate are classified as potent topical corticosteroids. Fluticasone propionate is a newer type of topical corticosteroids and has high topical anti-inflammatory effects and a low potential to cause adverse effects because of low systemic absorption and rapid metabolism and clearance.⁵⁻⁹ This trial aimed to evaluate further the use of fluticasone propionate twice weekly as part of an emollient based maintenance regimen in patients with moderate to severe atopic dermatitis.

Patients and methods

This was a randomised, double blind, placebo controlled, parallel group, European study. Patients (age 12-65 years) with recurrent moderate to severe atopic dermatitis were eligible for the study and were recruited during a flare of atopic dermatitis (see assessments for definition).¹⁰ This was assessed from an index lesion (a typical lesion on the patient's neck, hands, or flexural sites of the elbows or knees). We excluded patients with any medical condition for which topical corticosteroids were contraindicated, those with other dermatological conditions that may have prevented accurate assessment of atopic dermatitis, and those

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receiving any concomitant medications that might have affected the study's outcome.

Treatments

Initially the flare was stabilised with fluticasone propionate cream 0.05% or fluticasone propionate ointment 0.005%, once or twice daily, for four weeks. Patients who achieved remission (see assessments) then entered a maintenance phase and, using the same formulation as in the stabilisation phase, applied fluticasone propionate or its placebo base on two successive evenings per week for up to 16 weeks. They applied treatment to all healed sites of potential relapse and any newly occurring sites. In addition, patients in both treatment groups routinely applied emollient twice daily (once on treatment days) and used a bath oil as needed.

Assessments

Atopic dermatitis was assessed by using the three item severity (TIS) score (the sum of three signs: erythema, oedema or papulations, and excoriations; each scored 0=absent, 1=mild, 2=moderate, or 3=severe).¹¹ We defined a flare or relapse as a score of 4 or higher. At the start of the study, for recruitment purposes, an index lesion was assessed, but during the maintenance phase a flare occurring at any site was to be assessed. We defined remission or control as an index lesion score of 1 or lower. Patients were assessed every two weeks in the stabilisation phase and after two, six, 10, and 16 weeks in the maintenance phase. At each visit patients were questioned about adverse events, and the investigator recorded these. In addition patients had regular examinations for visual evidence of skin atrophy.

Analysis

The primary end point was the time to relapse of atopic dermatitis during the maintenance phase. We used regression analysis to compare treatment groups, using terms for country, frequency of treatment in the stabilisation phase, age, and sex. We used the Kaplan-Meier product limit method to estimate the distribution of time to relapse of atopic dermatitis, and we calculated summary statistics such as median time to relapse and proportions of patients who were relapse free from the estimates. We also determined the secondary end point, the proportion of patients with controlled atopic dermatitis at the end of the stabilisation phase.

Results

Accountability and demographics of patients

We recruited and screened a total of 376 patients (171 male, 205 female) from 39 centres in six countries from January 1998 to July 1999 (see bmj.com). After the condition had been stabilised by regular daily treatment with fluticasone propionate, 295 patients continued into the maintenance phase (33 discontinued, 48 did not meet eligibility criteria). After 16 weeks the disease remained controlled in 133 patients (87 using fluticasone propionate twice weekly, 46 emollient alone), 135 patients (40 fluticasone propionate, 95 emollient alone) had experienced a relapse, and 27 patients had discontinued.

The table shows results for the primary end point. For the cream formulation we found a significant (P<0.001) difference in time to relapse of atopic dermatitis during the maintenance phase, with a hazard ratio of 5.8 (95% confidence interval 3.1 to 10.8). The median time to relapse on twice weekly fluticasone propionate exceeded 16 weeks (the duration of the study), whereas on emollient alone it was 6.1 weeks (fig 1).

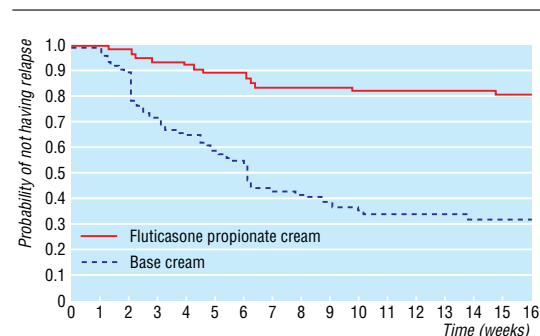


Fig 1 Kaplan-Meier plot showing the probability of remaining free from relapse during the 16 week maintenance phase. In the double blind study, twice weekly fluticasone propionate cream or its base (placebo) was used in addition to maintenance treatment with emollients

For the ointment formulation, the difference that treatment made was also significant (P=0.010), with a hazard ratio of 1.9 (1.2 to 3.2). The median times to relapse on ointment were similar to the times achieved on cream (table and fig 2).

In comparison with fluticasone propionate cream twice weekly, more patients applying fluticasone propi-

Summary of analysis of time to relapse in the maintenance phase

	Group using cream		Group using ointment	
	Daily emollient* plus twice weekly fluticasone propionate (n=70)	Daily emollient* plus twice weekly base (placebo) (n=84)	Daily emollient* plus twice weekly fluticasone propionate (n=68)	Daily emollient* plus twice weekly base (placebo) (n=73)
No (%) of patients having a relapse	13 (19)	54 (64)	27 (40)	41 (56)
% difference between placebo and fluticasone propionate (95% CI)	46 (32 to 59)		16 (0.2 to 33)	
Median time to relapse in weeks	>16	6.1	>16	6.1
Hazard ratio (base:fluticasone propionate)†	5.8 (95% CI 3.1 to 10.8, P<0.001)		1.9 (1.2 to 3.2, P=0.010)	
Number needed to treat‡	2.2		6.1	

*Twice daily (once daily on study treatment days) plus bath oil as required.

†Based on the probability of a relapse occurring at any time point in the study, on one treatment relative to the other.

‡Number of patients who have to be treated with fluticasone propionate to prevent one relapse that would have occurred on placebo.

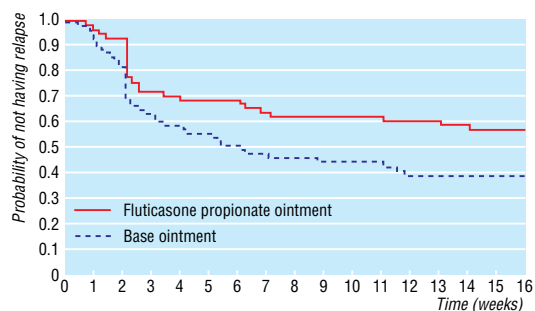


Fig 2 Kaplan-Meier plot showing the probability of remaining free from relapse during the 16 week maintenance phase. In the double blind study, fluticasone propionate ointment or its base (placebo) was used twice weekly in addition to maintenance treatment with daily emollients

onate ointment twice weekly had experienced a relapse by 16 weeks (19% *v* 40%). The difference between the two formulations was significant ($P=0.002$), with a hazard ratio of 2.9 (1.5 to 5.9). Only seven patients (six using emollient alone) experienced a relapse at a new site.

Analysis of data from the stabilisation phase showed no significant difference between application once and twice daily ($P=0.546$ for fluticasone propionate cream and $P=0.249$ for fluticasone propionate ointment).

Adverse events

The most common adverse event was ear, nose, and throat infection, which occurred in nine subjects during the stabilisation phase. Four adverse events were classified as serious (an episode of erysipelas, an exacerbation of asthma, and two flares of eczema). There was only one newly observed visual sign of skin atrophy related to study treatment, and this was during the stabilisation phase.

Discussion

Fluticasone propionate cream or ointment, added twice weekly to maintenance treatment with emollients only, reduced the risk of relapse in patients with atopic dermatitis. This study is one of the few randomised, controlled, clinical trials to examine longer term management of moderate to severe atopic dermatitis. For fluticasone propionate cream, the risk of relapse was reduced to approximately one sixth, and for fluticasone propionate ointment it was reduced to approximately half. Although the median time to relapse for patients using emollient alone was approximately six weeks, the median time to relapse for patients adding fluticasone propionate twice weekly was substantially longer and in excess of 16 weeks (study duration). Crucial to the success of the twice weekly maintenance treatment was the initial stabilisation of an acute flare by regular daily treatment with fluticasone propionate (for up to four weeks). We found no evidence that the frequency with which fluticasone propionate was applied (once or twice daily) in the stabilisation phase affected the outcome in the maintenance phase.

All treatment regimens were equally well tolerated, with only one reported drug related visual skin change

What is already known on this subject

Atopic dermatitis is characterised by frequent, unpredictable relapses, and there is little evidence to support any of the commonly used practices for long term maintenance treatment of moderate to severe cases

What this study adds

After stabilisation of an acute flare, adding fluticasone propionate cream or ointment twice weekly to daily emollient treatment significantly reduced the risk of patients experiencing a further relapse and extended remission time

This regimen seemed to be well tolerated, with a low risk of local adverse effects, and may paradoxically be steroid sparing since, by producing longer remission periods, it should reduce the need for intensive treatment with topical corticosteroids as is often required to control flares

(telangiectasia during the stabilisation phase) over 20 weeks. Previous studies have shown that fluticasone propionate has low atrophogenic potential and does not significantly affect the hypothalamic-pituitary-adrenal axis⁴⁻⁹ although we did not assess these in this study.

This is the first study to compare both fluticasone propionate cream and ointment in one clinical trial. Although the concentrations of the two preparations differed they were specifically formulated to show equivalent potency as determined by the established vasoconstrictor assay.¹² However this may not totally reflect performance in treating healed and active lesions of atopic dermatitis. In addition, although ointments are generally thought to be more effective than creams because of their occlusive properties, which enhance drug penetration, patients often find them messier to use and less cosmetically acceptable than creams.^{13 14} This may well have affected patients' compliance with the ointment; we monitored adherence to treatment by means of patients' daily diaries, but tube weights were not recorded. The unexpected difference between formulations requires further investigation.

This treatment regimen for fluticasone propionate may paradoxically be steroid sparing in patients with atopic dermatitis. It produces longer remission periods and should therefore reduce the number of acute, intensive courses of treatment with topical corticosteroids that are often required to control flares. In addition, by maintaining remission in the longer term, application of fluticasone propionate twice weekly will be limited mainly to previously healed sites, which are less permeable than inflamed lesions, and so the overall exposure to topical corticosteroids will be reduced even further. The use of the simple three item score system for monitoring the severity of atopic dermatitis will help doctors in deciding the best time to implement the twice weekly maintenance treatment. Whether or not this maintenance treatment strategy can be applied to other topical

corticosteroids of lower potency remains to be established.

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Getting back into medicine

Over 16 years ago I walked away from my first and last senior house officer post and into a very different career as a church minister. My husband and I had accepted an offer to train together, and I welcomed the chance to develop a more holistic approach to serving my fellow man. In the wake of much consternation from family and friends, I thought I might return after some months or possibly a few years. I kept my stethoscope, ophthalmoscope, and tourniquet at the back of my underwear drawer ... just in case.

Well, the years have rolled by. I've had two children who are now teenagers. I've worked in numerous places around England, travelled abroad, and helped build churches in several different settings. I've been a consumer of medical services, not a provider. I've been a typical anxious patient, wife, parent, daughter, and minister to sick loved ones. Apart from customary trips to the family doctor while growing up, I'd never been on the other side of the examining couch until I had my first child.

As my children reached their teens I realised that for the first time in years I had a little spare brain capacity. This had all but vanished in the earlier years of juggling child rearing with my new career and marriage. I was not quite so worn out all the time. I recalled the buzz of "the diagnostic challenge," the excitement of spotting something amiss before anyone else. The sense of satisfaction of minor surgery. I started to wonder if there was any possibility of returning to medicine in some capacity.

I talked to friends in medicine, I made multiple phone calls, and I prayed for an open door. Assorted obstacles appeared, none insurmountable. A few weeks later the postgraduate dean approved me for the flexible careers scheme. He encouraged me when he said I had "good transferable skills." I started reading

like mad. More phone calls and appointments have led to the confirmation of a supervised post as a supernumerary senior house officer in care of elderly people at my local teaching hospital. I am astonished.

My husband is supportive; so are the kids. My son can't wait to hear gory stories such as the ones I used to tell him about from my earlier days in accident and emergency medicine. My daughter is hoping my new career will bring about a rise in pocket money.

I have dug out my stethoscope from the back of my underwear drawer. It needed a little WD 40 to get it going. (The ophthalmoscope was destroyed long ago by little fingers.) Next month I will start my post, and I am really excited. And terrified.

Medicine and the NHS have changed a lot in the past 16 years. I think I still recognise the fundamental basics, however. I don't just want to be a doctor again. I really hope I can bring something positive with me as a result of my professional and personal experiences. I could do a lot with a soap box right now, but maybe I just ought to focus on getting my clinical skills up to speed. I'm not sure where the road will lead or how long it will take, but I'm happy and grateful to take it step by step.

Penny Cox, *Harrow, Middlesex HA3 7TE*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake, or any other piece conveying instruction, pathos, or humour.* If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.