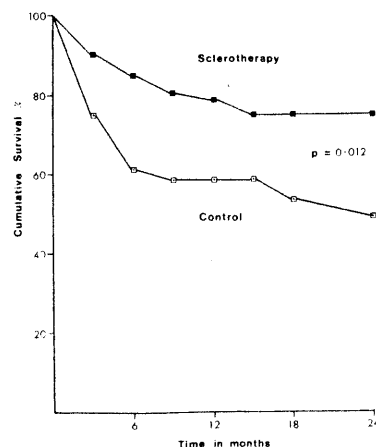




Cumulative survival in sclerotherapy patients (n=51) and controls (n=56) for the duration of the trial.

the ulcer was completely healed within a month of documentation and after treatment with cimetidine. In the other 2 patients the ulcers were slower to heal, taking 3 and 4 months, respectively, and in 1 of these there were further episodes of variceal bleeding during this period.

Of the 9 patients in whom strictures developed, 5 had dysphagia, 3 had strictures noted during the healing of oesophageal ulcers, and 1 was found to have a stricture at routine follow-up endoscopy. In those known to have had an ulcer previously, strictures developed in 2 within a month of healing, and in the other after 4 months and a further 4 courses of sclerotherapy. Strictures were never encountered with fewer than 3 courses of injections (range 3-7), and in 6 patients no preceding oesophageal ulcer was documented. Dilatation of the stricture was necessary in 4 patients with persistent dysphagia. 2 patients required only one dilatation, and the other 2 needed two and four dilatations.

Perforation of the oesophagus, confirmed by 'Gastro-graffin' swallow, was seen in 2 patients, both of whom had severe persistent retrosternal pain and dysphagia immediately after sclerotherapy. The patient who died was one of the early patients in the series in whom a rigid oesophagoscope had been used. The tear in the other patient was at the site of an unsuspected high-oesophageal pouch, and the perforation healed with conservative management.

Discussion

This is the first clinical trial to show that control of bleeding from oesophageal varices in patients with cirrhosis can significantly improve survival. Although risk of further haemorrhage is low after shunt surgery, the various controlled trials carried out have all shown that this is matched by an increase in morbidity and mortality from portosystemic encephalopathy and liver failure, secondary almost certainly to the deprivation of portal venous blood.⁴⁻⁶ In contrast, sclerotherapy has no secondary effects on hepatic function, and with the significantly fewer deaths from bleeding the long-term survival rate is improved.

As shown by the present results, it is important to continue with courses of sclerotherapy until varices are obliterated and

the risk of haemorrhage thereby almost eliminated. Similar results were reported by Terblanche et al.⁷ and, in 4 of 6 patients in their series in whom sclerotherapy was used only as an emergency procedure, further multiple episodes of variceal bleeding occurred because sclerotherapy had not been continued until the varices were completely obliterated.

Our own experience of emergency endoscopy for variceal haemorrhage has confirmed that even with extensive gastro-oesophageal varices the site of bleeding is invariably from varices at or just above the gastro-oesophageal junction, and it is these only which we aim to obliterate. In over 60% of our patients obliteration of varices was achieved within a 3-month period after 3 or 4 courses of injections, and of the patients followed up for at least a year after successful obliteration of varices, 64% showed no recurrence and only 2 patients had further episodes of bleeding associated with reappearance of varices. Follow-up endoscopy is likely to be necessary at intervals of 9-12 months after initial obliteration of varices so that reinjection can be carried out if recurrence of varices is found.

Terblanche et al.⁷ have described the disappearance of gastric varices after sclerosis of distal oesophageal varices, presumably as a result of retrograde propagation of thrombus, but in the present series there were 2 patients in whom oesophageal varices were satisfactorily obliterated who were subsequently admitted to hospital with bleeding from gastric varices. In both patients gastric varices were present before sclerotherapy, and there are some patients with portal hypertension and oesophageal varices in whom bleeding occurs only from gastric varices.⁸ We have not seen gastric varices developing after the sclerosis of distal oesophageal varices, and the possibility that obliteration of the oesophageal varices results in a rise in portal pressure sufficient to increase the risk of bleeding from gastric varices seems most unlikely.

Although there is some argument for shorter intervals between injection courses during the period of variceal obliteration, because the risk of early recurrent bleeding would thereby be reduced, the frequency of complications, especially oesophageal ulceration and stricture formation, is likely to be greater. Our initial experience with emergency sclerotherapy,⁹ in which injections were carried out over 1-3 weeks, showed extensive oedema and inflammation of the lower oesophagus. Injection of sclerosant under these conditions is liable to cause necrosis, ulcer formation, and further bleeding. In addition, the longer interval of 3-4 weeks between courses of injections allows patients to return home and improves compliance—a notable feature of the present trial.

The poor results of shunt or oesophageal transection procedures in patients with decompensated hepatic function—category C—are well known,^{2,10,11} and in the controlled trials of portacaval shunt these patients were excluded. The present results of injection sclerotherapy in this group are most encouraging: the risk of rebleeding was reduced to the same level as in the less severely affected patients in categories A and B, and a trend towards increased survival has reached the 7% level of significance. This supports a clinical impression that in some category-C patients prevention of further bleeding has allowed liver function to recover and prolong survival. Injection sclerotherapy has proved a well-tolerated procedure which is effective in preventing rebleeding and is without a significant mortality of its own.

In many of the previous clinical trials of treatment for variceal haemorrhage, the major group of patients included had alcoholic cirrhosis and, as Saunders et al.¹² have pointed

out, the results will also be affected by the natural history of this condition, particularly if the patient continues to drink. Indeed, the close supervision of our patients during the trial could have resulted in a significantly greater number abstaining from alcohol, but this applied to both the sclerotherapy and the control groups. We found no difference in the frequency of rebleeding between alcoholic patients who either continued to drink or stopped drinking and patients with non-alcoholic cirrhosis either in the sclerotherapy or control group.

The use of the flexible oesophageal sheath, developed at King's College Hospital by Williams and Dawson,³ has certain advantages. Protrusion of the varices through a distal window with compression above and below provides easy access for injection: the gastro-oesophageal junction can be readily identified before injection of sclerosant. After injection the varix may be further compressed by rotation of the sheath, and immediately after the procedure none of our patients has required passage of a Sengstaken tube to control bleeding. The sheath used in conjunction with general anaesthesia lessens the risk of pulmonary aspiration during the procedure. However, injection of varices without a sheath and with simple sedation, as in routine endoscopy, is undertaken by other groups¹³ (and by us in selected patients—usually those with limited residual varices after previous injection). Another variation of the technique is to use multiple submucosal injections between varices¹⁴ rather than direct injection into the varices. In our experience accurate siting of the injections can be difficult, especially with local movement of the gastro-oesophageal junction even with the use of heavy sedation and antispasmodics. Several centres continue to recommend the rigid oesophagoscope,¹⁵⁻¹⁷ particularly for emergency sclerotherapy, the advantage being that this instrument can be easily manoeuvred to compress actively bleeding varices during the stage of injection. However, the rigid oesophagoscope carried a much greater risk of oesophageal perforation.^{16,17} In general, we prefer to control haemorrhage with oesophageal tamponade before proceeding to injection sclerotherapy, since accurate positioning of injections is then easier.

Although studies of oesophageal function after injection sclerotherapy have shown diminished motility with reduction of lower-oesophageal sphincter pressures which may result in an increased susceptibility to oesophageal reflux,¹⁸ symptoms of this condition have not so far been a practical problem in any of our long-term patients. Follow-up endoscopy has, however, shown acute inflammation of the distal oesophagus in several patients, and oesophageal ulceration and strictures do occur with repeated courses of injections in a significant number of our patients, although about half of these patients remain without symptoms. Ulceration and strictures may result from inadvertent reinjection of already sclerosed vessels, with consequent submucosal leakage of sclerosant. The oesophageal ulcers have invariably healed, and the main cause for concern has been the occurrence of bleeding from the site of ulceration or from remaining varices during delay before reinstitution of sclerotherapy.

We thank the many physicians and surgeons who have referred patients for their collaboration in the running of this trial, and the nursing staff for their willing help. We are grateful to Dr J. Saunders for the statistical analysis.

Correspondence should be addressed to R. W., Liver Unit, King's College Hospital Medical School, Denmark Hill, London SE5 8RX.

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BASOPHILS IN ALLERGEN-INDUCED PATCH TEST SITES IN ATOPIC DERMATITIS

E. BRUCE MITCHELL
MARTIN D. CHAPMAN
F. MICHAEL POPE

JULIE CROW
SUKHINDER S. JOUHAL
THOMAS A. E. PLATTIS-MILLS

Clinical Research Centre, Northwick Park Hospital,
Harrow, Middlesex

Summary Atopic dermatitis often occurs in patients who have high IgE levels and positive immediate skin tests to several common allergens. However, there is considerable doubt about the role played by allergens in this disease. Patch testing for 48 h at superficially abraded skin sites revealed that allergens could induce eczematous lesions in atopic dermatitis patients but only in those who also gave a positive immediate skin reaction to the same allergen. Lesions induced by the purified house dust mite antigen, antigen P₁ contained mononuclear cells, basophils, eosinophils, and neutrophils. These patients also had raised specific serum IgE against antigen P₁, and their leucocytes released histamine upon exposure to the same antigen. Thus an acute eczematous lesion can be induced by the application of inhalant allergens to the skin.

Introduction

ATOPIC dermatitis is a common debilitating skin condition occurring in all age-groups, though predominantly in the young. Most patients have high IgE levels and positive immediate skin tests to several inhalant allergens.^{1,2} They also often have allergic rhinitis, asthma, and/or food allergy.

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Skin affected by eczema is infiltrated with mononuclear cells, which suggests that the condition may be a form of delayed hypersensitivity (DH). However, allergens that cause immediate responses do not usually give rise to DH skin lesions. This failure of allergens to produce delayed or eczematous lesions has often been given as a reason for not regarding allergens as an important cause of eczema.^{3,4} However, the very small quantities of antigen used in skin testing atopic patients, or the local effects of vasoactive amines, may be why DH responses do not develop.⁵ Another reason may be the reported impairment in these patients of cell-mediated immune responses to candida and tuberculin.⁶

Patients with atopic dermatitis often improve after admission to hospital, even though treatment is not changed.⁷ Many of these patients are sensitive to allergens derived from the house dust mite *Dermatophagoides pteronyssinus* and are exposed to high levels of these allergens at home,^{8,9} but not when they are in the relatively dust-free environment of a hospital. We therefore decided to re-investigate the effects of exposure of the skin to dust mite and other allergens.

Materials and Methods

Seventeen patients (aged 7–61) with severe atopic dermatitis were skin tested (by prick technique) with a variety of common inhalant allergens (Bencard Ltd., U.K.). These same allergens and extracts of floor dust were dialysed against saline before being used for patch testing. Antigen P₁ was purified from an extract of *D. pteronyssinus* culture by concentration over an 'Amicon PM10' filter, fractionation on 'Sephadex G-100', and 'pevicon' block electrophoresis.¹⁰ Controls consisted of ten non-allergic volunteers with negative prick tests and six volunteers who had a history of rhinitis or asthma and positive prick tests but no history of atopic eczema.

Patients were only patch-tested when their dermatitis was in remission, and tests were done on skin that was macroscopically normal. A 2 cm × 2 cm area of skin was gently abraded by removing the upper layers of the epidermis but without causing capillary bleeding. 0.5 ml of aqueous allergen or normal saline was applied with a pad of sterile gauze, the area was occluded, and the dressing retained with hypoallergenic tape. Lesions were generally inspected at 48 h, when a biopsy specimen was also taken by the use of a 4 mm disposable biopsy punch (Stiefel Laboratories U.K. Ltd.). Care was taken to infiltrate local anaesthetic around the biopsy site but not into it. The biopsy specimens were immediately placed in Karnovsky's fixative.¹¹ After 24 h they were washed in four changes of 0.1 mol/l sodium cacodylate pH 7.4 (Sigma) at 4°C and dehydrated in varying concentrations of alcohol. Specimens were embedded in hydroxyethyl methacrylate and 1–2 µm sections were stained with Giemsa.¹² All sections were approximately 4 mm × 2 mm, and the whole area was examined, the few cells in the epidermis and on the surface not being counted.

Total serum IgE levels were measured by double antibody inhibition radioimmunoassay, and specific antibodies to antigen P₁ of both IgE and IgG isotypes were assayed by the use of an antigen-binding radioimmunoassay technique.^{13,10} Tests for in-vitro leucocyte histamine release in response to antigen P₁ were done for all subjects.¹⁴ Dust samples were collected from the homes of the patients tested and assayed for antigen P₁ content.⁹

Results

Patch testing with allergens in seventeen atopic dermatitis patients produced a positive macroscopic response after 48 h in 38 out of 38 tests (table 1). These lesions were evident at 24 h and progressed until 72 h. Most of the positive patches showed confluent papular erythema (++) while the stronger responses also showed oedema and exudation (+++). Scaling

TABLE I—PATCH TESTS IN ATOPIC DERMATITIS PATIENTS AT 48 HOURS*

Macroscopic† appearance‡	No. of responses with antigen giving positive prick tests‡	No. of responses with antigen giving negative prick tests§	No. of reactions with normal saline
+++	7	0	0
++	26	1	0
+	5	1	4
±	0	2	9
0	0	5	10

*Seventeen patients tested with a variety of common inhalant allergens. Several of the patients were tested on more than one occasion.

†0 = no reaction; ± = erythema covering <10% of the patch area; + = patchy erythema with occasional papules; ++ = confluent papular erythema with or without a mild exudate; +++ = as ++ but with exudation, oedema, and extension beyond the patch area.

‡Allergens included grass pollen, cat dander, guinea pig dander, floor dust, *D. pteronyssinus* extract, and antigen P₁.

§Ragweed extract (Greer Laboratories Inc., Lenoir, North Carolina).

occurred in most lesions as they resolved over 4–10 days. Most patients were tested with more than one allergen, including extracts of house dust mite, grass pollen, guinea pig dander, cat dander, and their own floor dust. Saline produced patchy erythema (+) on four occasions, and no reaction (0 or ±) in 19 patch tests on the same patients. These patients, who lived in England, had not been naturally exposed to ragweed pollen, and showed negative immediate skin tests with ragweed extract. In seven out of eight cases no striking response to patch tests with ragweed extract was demonstrable.

Ten patients were tested with the purified dust mite allergen, antigen P₁. All ten showed positive patch responses to the 5 µg dose (in preliminary experiments we found that 0.05 µg would elicit a mild reaction), while nine out of ten non-allergic controls showed no reaction (table II). The ten patients had marked immediate hypersensitivity to antigen P₁ as judged by the intradermal skin test and in-vitro leucocyte histamine release (table II); they also had high levels of serum IgE and IgG antibodies against antigen P₁ (table III). Total serum IgE levels were very high in the patients with atopic dermatitis (geometric mean 5460 IU/ml), which was in keeping with the fact that most of these patients had had extensive skin involvement within the previous 6 months (table III). Six dust-mite-allergic individuals who did not have dermatitis were also patch-tested with antigen P₁ and four of them showed positive responses (table II).

Histologically the positive patches induced with antigen P₁ showed a moderate to severe dermal inflammatory cell infiltrate most prominent around blood vessels. This contrasted with the scarcity of inflammatory cells in the responses to saline in nine out of ten of these patients and in the responses to the allergen in nine out of ten of the non-allergic controls. In biopsy specimens of positive lesions taken at 48 h the epidermis contained occasional inflammatory cells. At 72 h epidermal changes, including focal spongiosis and microvesiculation, were more evident. Differential cell counts done blind showed highly significant increases in the number of basophils in positive lesions (table IV)—e.g., the dermatitis patients showed a mean of 41 basophils in response to antigen P₁, while non-allergic controls had 1 (table IV). No differences in absolute mast cell counts were noted in the different groups. Eosinophils were a predominant infiltrating cell in the positive biopsies; they

TABLE II—RESULTS OF PATCH TESTS, INTRADERMAL SKIN TESTS, AND TESTS FOR LEUCOCYTE HISTAMINE RELEASE

Subjects	Patch test at 48 h		Intradermal skin test* (15 min) antigen P ₁ (µg/ml)	AgP ₁ leucocyte histamine release† (%)
	Antigen P ₁ (5µg)	Saline		
Atopic dermatitis (n=10)	++	—	10 ⁻⁵	32
	++	—	10 ⁻⁵	27
	++	±	10 ⁻⁴	56
	++	+	10 ⁻⁴	0
	++	+	10 ⁻⁵	47
	+++	—	10 ⁻⁶	20
	++	±	10 ⁻⁵	55
	++	—	10 ⁻⁵	34
	+++	±	10 ⁻⁶	34
	++	—	10 ⁻⁶	45
Atopic non-dermatitis (n=6)	—	—	10 ⁻⁵	45
	++	±	10 ⁻³	0
	+	—	10 ⁻⁴	16
	+	—	10 ⁻⁵	20
	±	±	10 ⁻⁴	31
	±	±	10 ⁻¹	0
Non-atopic controls (n=10)	—§	N.D.	<10 ⁻⁴ ¶	>100

Done with 0.02 ml of serial 10-fold dilutions of antigen P₁. A wheal of >6 × 6 mm was regarded as the endpoint. Skin tests negative at 10 µg/ml are recorded as 10⁻¹.

†Nine out of ten patients showed histamine release (>10% above background) with dilutions of antigen P₁ from 1 µg/ml to 10⁻⁶ µg/ml. Values shown are % release above background using 10⁻⁴ µg/ml.

‡Positive by prick test.

§One subject gave a (+) reaction and one gave a (±) reaction.

¶One subject positive at 1 µg/ml.

||One control showed 15–5% histamine release at 10⁻⁴ µg/ml. The other 9 controls had <10% release at concentrations up to 1 µg/ml.

were more numerous than basophils (table IV). Biopsy specimens of the positive lesions also showed mononuclear cell and neutrophil infiltration. For each cell type the number of infiltrating cells in reactions to antigen P₁ in atopic non-dermatitis controls was midway between that in the positive patient reactions and that in negative control reactions. Their characteristic ultrastructural features¹⁵ seen on electron microscopy confirmed the presence of basophils, mast cells, eosinophils, and neutrophils. A typical basophil in the skin is shown in the accompanying figure.

Discussion

Our study has shown that a modification of the usual method of presenting immediate hypersensitivity allergens can consistently induce an eczematous delayed skin response. The dose of allergen used was larger than that necessary to

TABLE IV—DIFFERENTIAL CELL COUNT OF INFILTRATING CELLS IN 1–2 µm SECTIONS OF SKIN BIOPSY SPECIMENS

Subjects	Patch test	Basophils	Mast cells	Eosinophils	Mononuclear	Neutrophils	Total
Atopic dermatitis (n=10)	Antigen P ₁	41 (17–96)	60 (29–94)	190 (67–541)	698 (461–1059)	53 (21–138)	1,149 (710–1858)
	Saline	2‡ (0–6)	52 (30–92)	11‡ (4–31)	366‡ (236–569)	17* (7–38)	462‡ (301–711)
Atopic non-dermatitis (n=6)	Antigen P ₁	12 (2–90)	65 (38–112)	24 (0–506)	455 (278–746)	787 (4–169)	787 (443–1400)
	Antigen P ₁	1‡ (0–4)	53 (31–92)	1‡ (0–2)	279‡ (166–468)	5‡ (1–16)	350‡ (212–577)

Histological sections examined were of similar size (4 mm width), and all cells infiltrating the dermis down to the level of the panniculus adiposus were counted. Results are expressed as geometric mean values. The figures in parentheses represent 1SD range above and below the geometric mean.

Results for antigen P₁ and saline patch sites in atopic dermatitis patients were compared by paired *t* test. Results for antigen P₁ lesions in atopic dermatitis patients and those in non-atopic controls were compared by an unpaired *t* test. Figures were converted to log values prior to statistical analysis. * *p* < 0.02; † *p* < 0.01; ‡ *p* < 0.001.

TABLE III—TOTAL SERUM IgE AND SPECIFIC ANTIBODIES TO ANTIGEN P₁

Subjects	Total IgE* (units/ml)	IgE anti P ₁ (binding activity)†	IgG anti P ₁ (binding activity)†
Atopic dermatitis (n=10)	5460 (2 065–14 435)	206 (44–978)	811 (321–1998)
Atopic non-dermatitis (n=6)	293 (137–625)	9 (1–52)	19 (2–164)
Non-atopic (n=10)	25 (13–50)	<3 (0)	5 (3–9)

*1 unit IgE was assumed to be equivalent to 2.4 ng.

†Results obtained from a control curve and expressed in arbitrary units of binding activity (1 BA unit ≡ 1 ng). Results are expressed as geometric mean values. Figures in parentheses represent one standard deviation range above and below the geometric mean. An unpaired *t* test was used to compare the results of both the patient group and the atopic non-dermatitis group with the non-atopic control group. All results were converted to log values before statistical analysis.

produce an urticarial wheal in the same patients, but it is similar to that used to elicit delayed hypersensitivity responses. Furthermore, we found that dust from the beds of eight of our patients contained high levels of antigen P₁ (50 ± 10.5, [SE] µg/g). Abrasion and prolonged exposure, both features of the technique used, simulate naturally occurring conditions, since scratching is an important feature of the disease and exposure to house dust allergens is likely to be prolonged and repeated.

The basophil infiltrate reported here is similar to that which occurs in induced contact dermatitis and in the late cutaneous response.^{16–18} Furthermore, electron microscope evidence of basophil degranulation, as has been reported in contact dermatitis,¹⁹ was present in some of the patch responses. The presence of basophils is interesting because these patients' leucocytes released histamine in response to the same antigen, and it is probable that the infiltrating basophils were sensitised to antigen P₁. The presence of basophils may also imply that sensitised T cells are involved in the skin response, since human T cells can release a basophil chemotactic factor.²⁰ Unlike induced contact dermatitis, the patch responses always showed a marked eosinophil infiltration.¹⁶ Recruitment of eosinophils into allergen-induced patch sites probably depends on the release of eosinophil chemotactic factor(s) from either mast cells or basophils. Neither basophils nor eosinophils have been reported to be increased in naturally occurring lesions of atopic dermatitis; however, it has been suggested that eosinophils may participate in the development of the lesions.²¹ The differences in histological findings between



Basophil

Under the electron microscope basophil leucocytes (magnif. $\times 12\,285$; bar = $1\,\mu\text{m}$) had multilobed nuclei, large variable granules (diam. $860\,\text{nm} \pm 226$), and knob-like surface protrusions. The granules (below) (magnif. $\times 48\,940$; bar = $0.2\,\mu\text{m}$) were particulate and had a variable number of myelinoid membranous figures.

atopic dermatitis and the patch test lesions may reflect three features of these patches. Firstly, they are of a known duration (48 h); secondly, they probably represent a fairly intensive local stimulation; and thirdly, they have not undergone the regular scratching which occurs with naturally occurring eczema and which may influence both dermal and epidermal histology.

The pathogenesis of atopic dermatitis is certainly multifactorial since in many patients stress, skin infection, contact sensitivity, and foods can cause exacerbations. Genetic factors, itch threshold, and abnormalities of autonomic responses may also be important.^{4,22} Although many recent workers have discounted the role of inhalant allergens, several early investigators considered that house dust, pollen, and animal dander allergens were an important cause of dermatitis.^{7,23} Our results support the view that inhalant allergens should be considered as a factor in the

disease in those patients who are sensitive to these allergens. Proof that any factor is important in atopic dermatitis can only be established by controlled avoidance and exposure experiments. However, the delayed nature of the response reported here might explain why patients are often unaware that a particular allergen exacerbates their eczema.

The patch test response to allergens has obvious parallels with cutaneous basophil hypersensitivity (CBH) in guineapigs²⁴—they both contain basophils and eosinophils, they have a similar time course, and they are elicited by similar doses of antigen. The basophils infiltrating guineapig lesions are known to be sensitive to the eliciting antigen and can release mediators locally.²⁵ It seems likely that as in guineapig CBH the response to allergens in our patients involves both T cells and anaphylactic antibodies, and that both lesions represent an overlap between immediate and delayed hypersensitivity.

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Correspondence should be addressed to F. B. M., Division of Immunology, Clinical Research Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

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DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF ERYTHROMYCIN FOR TREATMENT OF CAMPYLOBACTER ENTERITIS

BROWNEN J. ANDERS
JOHN W. PAISLEY

BRIAN A. LAUER
L. BARTH RELLER

Departments of Pediatrics and Medicine, University of Colorado School of Medicine, and Clinical Microbiology Laboratories, University Hospital, Denver General Hospital, and Children's Hospital, Denver, Colorado, U.S.A.

Summary Although most strains of *Campylobacter jejuni* are susceptible in vitro to erythromycin and the drug has been recommended for treatment of campylobacter enteritis, prospective controlled trials have not been done. Erythromycin (250 mg 6-hourly for adults and 40 mg/kg daily for children) has been compared with placebo in a double-blind trial of 5-day therapy for acute campylobacter enteritis. The mean number of days of illness at onset of therapy was 5.6 for the treatment group (n=15) and 6.5 for the placebo group (n=14). There were no differences in temperature, symptoms, and stool characteristics between the two groups. The mean duration of unformed stools after treatment was 4.1 days in the erythromycin group and 3.5 days in the placebo group. Fever, when present, abated within 48 h in all but two patients in each group. Follow-up faecal cultures 2 days after completion of therapy, however, were negative in all 15 of the erythromycin-treated patients compared with 6 out of 14 controls. Thus erythromycin promptly eradicates *C. jejuni* from the faeces but does not alter the natural course of uncomplicated campylobacter enteritis when therapy begins 4 or more days after the onset of symptoms.

Introduction

WITH the development of selective culture techniques *Campylobacter jejuni* has been shown to be a major cause of bacterial gastroenteritis and its incidence equals or exceeds that of salmonellosis or shigellosis in many parts of the world.¹ The proportion of stool cultures positive for *C. jejuni* from patients with enteritis has been reported to be 5–1% in Belgium,² 7–1% in the U.K.,³ and 5% in the United States.⁴ *C. jejuni* is usually susceptible in vitro to erythromycin.⁵ Some investigators have reported that the clinical course of campylobacter gastroenteritis is modified by erythromycin therapy,^{6,7} and many physicians have begun to use erythromycin to treat this disease. However, we know of no prospective clinical trials that prove the efficacy of erythromycin treatment. The purpose of this study was to determine the effect of treatment on acute campylobacter enteritis in a double-blind controlled clinical trial of erythromycin versus placebo.

Patients and Methods

Microbiology

All stool specimens of adequate volume submitted to the clinical microbiology laboratories of three Denver hospitals were examined for campylobacter by direct dark-field microscopy.⁸ Besides cultures for salmonella and shigella, all faecal specimens were plated on selective campylobacter blood agar plates,⁴ which were incubated at 42°C in a candle jar and examined daily for 3 days. Bacteria were identified as *C. jejuni* if they had typical darting motility and Gram stain characteristics, were positive for oxidase and catalase, grew at 37°C and 42°C but not at 25°C, and were susceptible to nalidixic acid.

Patients

As soon as direct dark-field examination or cultures were positive, patients were contacted, the study explained, and written consent obtained. Patients with positive dark-field examinations were subsequently excluded if their stool cultures were negative. Patients also were excluded who were already well or nearly well by the time they were contacted, who were receiving antimicrobials, who had mixed enteric infections, or who did not return for follow-up (n=3).

Antimicrobial Treatment

This was a double-blind placebo controlled study. Patients were randomised to receive either placebo or erythromycin (enteric-coated base tablets, 250 mg four times daily, for adults, or erythromycin ethylsuccinate suspension, 40 mg/kg daily in four divided doses for children) for 5 days.¹⁰ Erythromycin and placebo preparations were supplied by the Upjohn Co., Kalamazoo, Michigan.

Compliance was estimated by counting tablets or estimating the volume of suspension remaining after treatment. Good compliance was defined as no tablets (or suspension) remaining, fair compliance as fewer than 10 (or less than half), and poor compliance as more than 10 (or greater than half).

Clinical Data

Data collected at the initial interview included duration of illness, consistency and frequency of stools, presence of blood and mucus, history of fever, and presence of associated symptoms. Patients were advised not to use other antibiotics or antidiarrhoeal medication. Data sheets were given to the patients to be filled out daily for 5 days; the patient was asked to record daily temperature, stool characteristics (number, consistency, presence of blood and mucus), vomiting, abdominal pain, and all medications taken. Patients were telephoned at 3 days to encourage compliance. Stool cultures were repeated 2 days after completion of therapy at which time data sheets were collected and the amount of drug remaining was recorded. Patients were telephoned 1–3 months after treatment to determine if relapse had occurred.

Statistical Analysis

The significance of differences in outcome between the placebo and erythromycin treatment groups was assessed by Fisher's exact test.

Results

During the one year study period 32 patients were enrolled and 29 completed the study—14 in the placebo group and 15 in the erythromycin group. The two groups were comparable in age, sex, and duration and severity of illness before enrolment. There were no significant differences in the characteristics of pretreatment clinical course between the two groups (table). All patients were well within 5 days of beginning the therapy. The only difference in outcome between the two groups was the result of post-treatment stool cultures on day 7 (table). All 15 erythromycin-treated patients had stools negative for *C. jejuni* compared with only 6 of 14 (42%) placebo-treated patients ($p<0.001$).

6 and 4 patients in each group had good and fair compliance, respectively. 2 of 3 patients with poor compliance in the erythromycin treatment group discontinued the drug after 2 days because of gastrointestinal intolerance. Both of these patients had negative follow-up stool cultures despite discontinuing the drug early. There were no relapses in either group.

1 patient in the placebo group and 3 in the erythromycin group complained of gastrointestinal symptoms attributed to the medication.