

A Double-Blind Controlled Trial of Elemental Diet in Severe, Perennial Asthma

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In a double-blind controlled trial 41 hospitalized adults with severe, perennial asthma of unknown aetiology were allocated to either an antigen-free elemental diet (Vivasorb®) or control diet, i.e. blended ordinary hospital food, for 2 weeks. At the time of entry into the trial all patients were in an active but stable phase of the disease. Medical treatment was given throughout the study as clinically indicated. Peak expiratory flow was measured hourly during the daytime and patients noted their symptoms daily on an assessment form. Validation of variables according to a scoring system indicated that the elemental diet resulted in an improvement of the patients' asthma ($P < 0.05$). It is concluded that elemental diet may serve as a diagnostic tool for disclosing alimentary intolerance in patients with perennial asthma.

Key words: alimentary intolerance; asthma; elemental diet.

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Alimentary intolerance has been recognized by physicians for many years. Much controversy, however, exists about the nature and importance of adverse reactions to food and chemical additives in human diseases, and the whole spectrum of symptoms that may appear is not delineated. Asthma, atopic dermatitis, allergic rhinitis, angioneurotic oedema, headache, tension-fatigue syndrome and chronic diarrhoea are among the symptoms reported in some cases to be due to adverse reactions to food (3). Elemental diet has been used in selected patients at our department as a diagnostic tool when alimentary intolerance has been suspected to be the cause of various diseases. We report here a double-blind controlled trial designed to test whether or not elemental diet contributed to the well-being of patients with severe perennial asthma of unknown aetiology.

PATIENTS AND METHODS

Patients

41 hospitalized adult patients with asthma attending the allergy clinic were included consecutively into the trial when the criteria stated in Table 1 were fulfilled, and informed consent obtained. The definition of asthma was as follows: paroxysmal, preponderating expiratory dyspnoea, reversible after treatment with bronchodilator. The patients were in an active but stable phase of the disease. 23 females and 14 males, aged 17-73 years (mean 43 years) completed the trial.

The mean duration of disease was 11 years (range 1-45 years). On entering the trial 20 patients were being treated with corticosteroid, and the mean duration of permanent steroid treatment was 7 years (range 0.5 - 17 years).

Table 1
Criteria for selection of patients

<i>Absolute</i>
Definition* of asthma fulfilled
At least one attack daily
Perennial rhinitis and/or anamnestic
"food intolerance" and/or
angioneurotic oedema
<i>Relative</i>
At least one of the following:
Skin prick test positive ($\geq$ one of 42 food antigens)
Serum IgE elevated
Circulating eosinophils elevated
(> one sample)

* See text.

Table 2
Further allergological characteristics of the 41 investigated patients with bronchial asthma

	Number of patients
Perennial rhinitis	23
Skin-manifestations	10
Angioneurotic oedema	3
Gastrointestinal complaints*	8
"Food intolerance" (patients' information)*	11
Atopy in the family	20
Skin prick test positive ($\geq$ 1 HEP)** of	
food antigens	14
immediate reaction	10
late reaction	5
Circulating eosinophils raised	
(> 350 mill/l)	32
(> 1000 mill/l)	17
Serum IgE (PRIST)*** raised (> 260 U/l)	
(reference value from own lab.)	9

* See text.

** Histamine equivalent prick: The weal reaction was $\geq$ as histamine reference 1 mg/ml (2).

*** Paper radioimmunosorbent test (Pharmacia, Uppsala, Sweden).

The remaining patients had been treated intermittently with steroid. Further allergological characteristics are stated in Table 2. The gastrointestinal symptoms experienced by some patients include diarrhoea, vomiting, nausea or abdominal pains. "Food intolerance" is the information given by patients about the suspected connection between ingestion of certain food

elements and allergic symptoms. Prior to this trial all the patients had been thoroughly investigated for varying periods of time in our allergy clinic without the aetiology of their disease being confirmed. Most cases were thus conceived as "intrinsic asthma".

Study design

The investigation was planned as a double-blind study, allocating the patients at random to either a chemically defined, antigen-free elemental diet or a control diet, both given orally for 13 days. The elemental diet used was Vivasorb® without added taste (J. F. Phrimmer & Co, Erlangen, FRG) containing essential fatty acids, amino acids, glucose, simple carbohydrates, vitamins and trace elements (4,000–10,000 kJ/day). The only supplements allowed were mineral water and pure glucose ad libitum. The control diet comprised all dietary elements normally consumed by patients in our hospital. These foodstuffs and liquors were blended and diluted with water to mimic the elemental diet as regards appearance and taste, and stored frozen (-18°C) after microbiological control culture until used. Both groups of diets were supplied in opaque bags, and the patients themselves filled the opaque drinking cups. None of the patients had tasted Vivasorb® before the trial. To ascertain the double-blindness, patients and staff of the department were told that the aim of the study was a comparison of two similar regimens. Moreover, the diets were distributed daily from the hospital's kitchen by one of us (M.W.), a dietary assistant, who never saw the patients.

Concomitant medical treatment with neophyllin, terbutaline, salbutamol or prednisone were used throughout the trial, but altered as clinically indicated. In single cases there was a need for analgetics or hypnotics. Paracetamol, nitrazepam and apozepam in 2 mg tablets were used. Thus medicine containing preservatives, colours, flavour enhancers and salicylates were abandoned. Peak expiratory flow (PEF) (l/min) (highest of three values) was assessed hourly during the daytime. Assessment forms with information about given medical treatment were

Table 3
Activity scoring system

Drugs	Dose (mg)	Score
One inhalation of salbutamol	2.5	2
Terbutaline tablet	5	2
Proxyphylline tablet	400	2
Prednisone tablet	1	1
Aminophylline supp.	500	2
Aminophylline inj.	200	2
Aminophylline infus.	1000	4
Average score first 4 days		a
Average score last 4 days		b
Difference a-b score		y
Average PEF (l/min) first 4 days		c
Average PEF (l/min) last 4 days		d
Difference c-d in % $\times 3/4 =$		v
Final score Y + V =		x

Responders, improvement corresponding to ≥ 25 scores.

Non-responders, a final score < 25 .

completed daily. The prearranged scoring system (Table 3) was based on the amount of given medicine and breathing capacity. Venous blood for laboratory investigations including white-cell count, platelets, and eosinophils were obtained every other day in the morning. Serum IgG, IgA, IgM, IgE, α_1 -antitrypsin, orosomucoid, ESR, and forced expiratory volume in the first second (FEV₁) were estimated at the beginning and end of the treatment period.

Statistics

Comparison of the treatment scoring in the two groups of patients was evaluated by the Wilcoxon's rank sum test for unpaired data, and chi-square analysis with Yates' correction.

RESULTS

Of the 41 patients who entered the trial four were excluded as they could not accept the diets. Two of them had had Vivasorb and two the control diet. During the treatment period two patients went into asthmatic status and needed high dose steroid, and one patient got

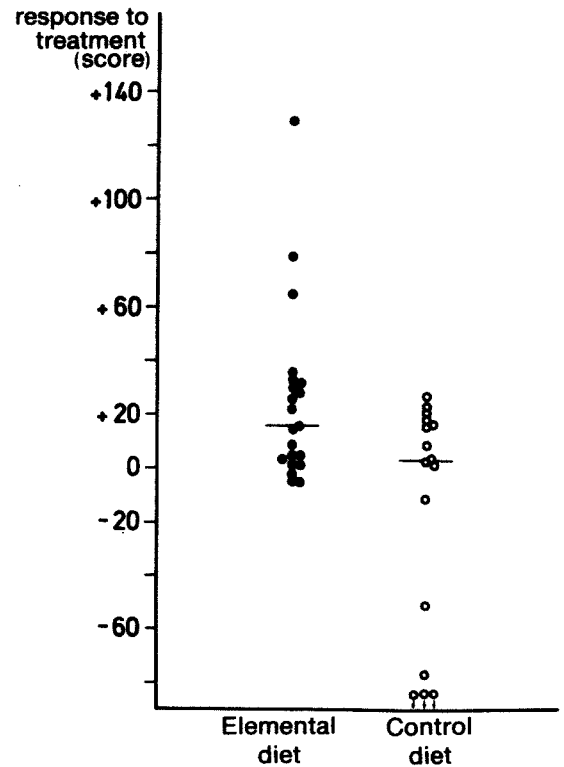


Fig. 1. Effect of elemental diet and control diet on severe, perennial bronchial asthma.

reversible respiratory and cardiac arrest (arrows in Fig. 1). These three patients had been given the control diet.

The patients given the elemental diet showed significantly more improvement than the patients given the control diet ($P < 0.05$) (Fig. 1).

Before breaking the code a score value (Table 3) of 25 was chosen arbitrarily as lowest level of improvement. According to this only one out of 16 patients in the control group improved compared with nine out of 21 on Vivasorb (responders), (χ^2 with Yates' correction = 0.42, $P < 0.05$). Although prednisone is known to induce eosinopenia, a 50% decrease of eosinophils in the blood of responders was seen during the test period when the prednisone dose was reduced (Table 4). FEV₁ also disclosed an improved breathing capacity in these patients. Such changes were not seen in non-responders or control patients. Concentrations of α_1 -antitrypsin, IgA, IgG, IgM, haemoglobin, orosomucoid and ESR were within normal limits in all patients, and the concentrations of white blood cells and platelets showed no correlation to activity of the disease.

Table 4

Correlations of eosinophils (mill/l), prednisone (mg) and FEV₁* (dl/sec) at the start (1) and at the end (2) of the treatment period, with elemental diet and control diet

	Vivasorb				Control	
	Responders (n = 9)		Non-responders (n = 12)		(n = 14)	
	1.	2.	1.	2.	1.	2.
Eosinophils mean (range)	962 (284–2288)	475 (195–1299)	506 (116–1163)	645 (100–1444)	740 (329–1847)	782 (257–2119)
Prednisone	13.2 (5–20)	9.3 (5–17.5)	9 (5–15)	8 (5–15)	6.6 (0–13)	7.5 (0–20)
FEV ₁	1.1 (0.7–1.6)	1.4 (0.7–1.8)	2.4 (0.7–2.4)	2.5 (0.8–2.1)	1.6 (0.7–2.7)	1.1 (0–2.4)

* Forced expiratory volume in first second.

DISCUSSION

Our initial aim in this trial was to assess whether orally administered antigen-free elemental diet could induce an improvement in severe, perennial asthma. Actually, more patients improved than expected by chance. The assessment was based on increased PEF and decreased need of medical treatment. The favourable changes of FEV₁, which increased 27 % during the 2-weeks test period, and the decrease of circulating eosinophils, in spite of the reduction of corticosteroid, support the good effect of the diet. In order to see if selection of patients expected to respond on antigen-free diet is possible, responders and non-responders given Vivasorb were compared. A shorter duration of disease was seen in responders, more of these patients were treated with steroid at the time of investigation and more often had very high counts of eosinophils and raised IgE. Skin prick tests with food antigens, however, revealed immediate reactions more often in non-responding patients. These observations are conflicting and possibly reflect the observations by Aas (1), who found that skin prick testing with food antigens is often unreliable. Our observations may indicate that responsiveness is best in patients treated early in the course of their disease and con-

comitant with corticosteroid. This may be substantiated by the presumption that immune complexes participate in the pathogenesis of chronic allergic disease (7), and abnormal levels of circulating immune complexes containing food proteins have recently been demonstrated in asthmatic patients with food intolerance (4).

Whether the symptoms are mediated by a reaginic, a non-reaginic, a non-immunological or mixed reaction will not be considered in this report. But the hypothesis that adverse reaction to food substances or additives are the provoking factors in some cases of severe perennial asthma have been supported by our observations.

After finishing the trial the responders were all provoked orally with benzoic acid, colours and different food substances, successively. Hereafter the single patients were advised to eat ordinary food without the alimentary substances now known to provoke asthmatic attacks. The provocations will not be commented in detail as they must be performed double-blinded, and this is the aim of a subsequent study.

We do find it of considerable interest that six of the responding nine patients were regarded as having "intrinsic asthma" or "eosinophil dyspnoea", as allergological investigations were

Table 5

Comparison of responders and non-responders on elemental diet

	Responders n = 9	Non-responders n = 12
Mean age years (range)	40 (22–55)	52 (17–67)
Females	4	6
Mean duration of disease (years)	8	12.5
Mean age at debut, years (range)	38 (17–63)	26 (2–50)
Patients in corticosteroid treatment	7 (77)**	3 (25)
Patients with other atopic symptoms	7 (78)	10 (83)
Patients with atopy in family	4 (44)	7 (58)
Mean PEF l/min (highest values)	414	496
Patients with pos. skin prick test*	3 (33)	8 (67)
Patients with pos. skin prick test immediate*	1 (11)	7 (58)
Patients with pos. skin prick test late*	2 (22)	2 (17)
Patients with eosinophilia	9 (100)	10 (83)
Patients with eosinophilia ≤ 1000 mill/l	3 (33)	6 (50)
Patients with eosinophilia > 1000 mill/l	6 (66)	4 (33)
Patients with raised serum IgE	4 (44)	2 (17)

* Food antigens.

** Percentage in parentheses.

Table 6

Eosinophilia, serum-IgE and skin-prick testing of asthmatic patients responding or non-responding to antigen-free diet

Patient No.	Eosinophilia (mill/l)		Serum-IgE > 260 U/ml	Skin prick test		
	< 1000	> 1000		Immediate	Late	
<i>Responders</i>						
3	+			+		
6		+				Intrinsic
11		+				Intrinsic
12		+			+	Intrinsic
26	+					Intrinsic
28		+	+		+	
29	+					Intrinsic
33	+		+			
40		+				Intrinsic
<i>Non-responders</i>						
2		+		+	+	
13	+					Intrinsic
15		+		+		
16						Intrinsic
17					+	Intrinsic
18	+			+		
25	+			+		
31			+			
32				+		
34		+				Intrinsic
36		+		+		
38	+					Intrinsic

negative, only revealing eosinophilia in the blood (Table 6). Among non-responders there were fewer "intrinsic asthma" cases. The possibility of a type-II error for the non-responders could be due to the rather short period of treatment in this trial.

As bronchial asthma continues to be a disease with considerable mortality, often in younger patients, in spite of the many new types of treatment (5, 6), the need to identify high-risk groups has been stressed (5). The group of asthmatics studied here certainly represent such patients, and on the basis of our findings we conclude that all perennial asthmatic patients investigated for provoking factors – including testing with classical elimination diets with negative results – should be tried with an antigen-free diet, preferably for 2–3 weeks, even if the patients present with little or no evidence of extrinsic aetiology.

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