Assessment of food chemical intolerance in adult asthmatic subjects

L Hodge, K Y Yan, R L Loblay

Abstract

***Background* – Identification of food chemical intolerance in asthmatic subjects can be reliably assessed by changes in the forced expiratory volume in one second (FEV_1) in response to double blind, placebo controlled challenges on a strict elimination diet. However, this method is cumbersome and time consuming. A study was undertaken to determine whether changes in bronchial responsiveness to histamine following food chemical challenge without an elimination diet might be a faster, more convenient method.**

***Methods* – Eleven adult asthmatic subjects were challenged twice with metabisulphite, aspirin, monosodium glutamate, artificial food colours, sodium nitrite/nitrate, 0.5% citric acid solution (placebo), and sucrose (placebo) on separate days. During the first set of challenges subjects consumed a normal diet. Bronchial responsiveness to histamine was assessed 90 minutes after each challenge. A greater than twofold increase in bronchial responsiveness was considered positive. For one month prior to and during the second set of challenges subjects followed a strict elimination diet and FEV_1 was monitored during and for two hours after each challenge. A fall in FEV_1 of 20% or more was considered positive.**

***Results* – Of the 77 food chemical challenges performed on an unmodified diet, 20 were positive (six placebo responses). In two subjects it was not possible to perform a histamine test after one of the chemical challenges because of poor spirometric function. Of the 77 food chemical challenges performed on an elimination diet, 11 were positive (no placebo responses). Excluding the two challenges in which there were no corresponding histamine tests, only on two occasions did the positive responses in both methods coincide, giving the unmodified diet method a sensitivity of 22%.**

***Conclusion* – Strict dietary elimination and measurement of FEV_1 after double blind food chemical challenge remains the most reliable method for the detection of food chemical intolerance in asthmatic subjects.**

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In clinical practice food is often cited by the asthmatic patient as a trigger factor. A recent survey of 99 patients with asthma in a Melbourne hospital has shown that 49% perceive that diet plays an important part in the control of their asthma.[1] In Christchurch, New Zealand, parents of 100 children with chronic asthma completed a questionnaire designed to determine the extent of food avoidance in children; 47% had either added or deleted a food because of the child's asthma.[2] It is unlikely that these perceived reactions are all IgE mediated since true food allergy occurs in less that 1% of the adult population and less than 5% of the paediatric population. An alternative explanation is that many of these asthmatic subjects may have experienced pharmacological side effects of natural or artificial chemicals contained within the foods.

Over the past decade more than 200 food sensitive adult asthmatic patients have been investigated for intolerance to food chemicals at Royal Prince Alfred Hospital, Sydney and the resulting dietary modifications have produced significant improvement in symptom control for these patients. The method of testing involves the use of an elimination diet for 4–6 weeks prior to double blind challenging with food chemicals suspected of causing exacerbations of asthma, firstly, to confirm that the symptoms are diet related by observing clinical improvement in symptoms and, secondly, to stabilise background symptoms so that challenge reactions can be more reliably interpreted.[3] Although effective, this method generally takes 3–4 months to complete and is very inconvenient for the patient due to the dietary restrictions required throughout this time. For this reason it would be useful to develop a diagnostic method of assessing food chemical intolerance in asthmatic subjects which is at least as reliable but does not require the subject to follow a highly restricted diet.

It has been suggested that, in food sensitive asthmatic subjects, bronchial responsiveness to histamine may increase significantly following challenge with foods or food chemicals.[4–6] Our own preliminary findings have documented reduced bronchial responsiveness to histamine when food chemicals, to which a sensitivity has been demonstrated, are removed from the diet.[7] It therefore seemed possible that a test of bronchial responsiveness to histamine following a food chemical challenge may be a sensitive and rapid technique for diagnosis of food chemical intolerance in the absence of prior dietary restriction.

Thus, the aim of this study was to compare the diagnostic value of food chemical challenge on an unmodified diet using histamine inhalation testing to assess reaction, with our usual method of challenge on a strict elimination diet using forced expiratory volume in one second (FEV_1) as the method of assessment.

Methods

SUBJECTS

Eleven asthmatic subjects (eight women) aged between 21 and 51 years (mean 38.2) who were referred to the Allergy Clinic at Royal Prince Alfred Hospital, Sydney, took part in the study. The subjects were assessed by a respiratory physician and a dietitian before admission into the study. No subject suffered from a clinically significant disease other than asthma, eczema, or rhinitis. The subjects were considered by the respiratory physician to be in a stable condition with regard to their symptom control. All subjects took regular medication for asthma although no subject was taking oral steroids during the study or for a minimum of two months previously. Asthma medications remained constant throughout the study except immediately before histamine or food chemical challenges. At these times subjects withheld aerosol bronchodilators for at least six hours, theophylline for at least 12 hours, and, when a histamine inhalation test was to be performed, antihistamines for at least 72 hours before testing. Each subject had previously reported exacerbations of their asthma after ingestion of one or more foods. None of the women was pregnant or lactating during the study and no subjects were current cigarette smokers.

ETHICAL APPROVAL

Ethical approval was obtained from the human ethics committee of Central Sydney Area Health Service which is constituted and functions in accordance with the National Health and Medical Research Council statement on human experimentation and supplementary notes. Subjects gave written informed consent.

STUDY DESIGN

The study was a crossover trial comparing two methods of double blind, placebo controlled food chemical testing which took between four and six months for each subject to complete. In order to compare the two methods each subject was challenged with a full set of food chemicals twice, initially on an unmodified diet and subsequently on the elimination diet (see below). Crossover sequences were not randomised as prior experience has shown that, once on a modified diet, subjects often do not return to their previous eating habits. Before commencing the challenges, asthma stability was ascertained by two histamine inhalation tests separated by two weeks. If these inhalation tests were within one doubling dose, the subject was deemed to be in a stable condition.

Once stability was established, the subjects commenced the first set of challenges. At this time they had been given no dietary advice and were encouraged to eat normally. Challenges were administered in graded doses as outlined below. Each challenge was followed with a histamine inhalation test 90 minutes after the last dose. If FEV_1 dropped by 10% or more during the challenge no further doses were taken of that food chemical. The criterion of a 10% reduction in FEV_1 for cessation of further doses was arbitrarily chosen. Less than 10% variation is not uncommon in repeated FEV_1 measurements. However, a decline in FEV_1 of 10% or more could indicate that the subject may be showing signs of a reaction to the chemical. It was important in the first set of challenges that a full blown reaction was avoided where possible because it would not be possible to perform a histamine inhalation test if the FEV_1 fell by 20% or more.

After completion of the first set of challenges the subjects began a strict elimination diet which was continued until completion of the second set of food chemical challenges. The second set of challenges was begun after four weeks on the elimination diet. In this arm of the study challenge responses were assessed only by measurement of FEV_1, as is our routine clinical practice. Administration of graded doses was halted only if FEV_1 fell by 20% or more, this being regarded as a positive challenge result. A histamine inhalation test was not performed after the challenge and FEV_1 measurements were continued at half hourly intervals for two hours after the last dose was taken.

FOOD CHEMICAL CHALLENGES

The chemicals tested were as follows (with graded doses in brackets): acetyl salicylic acid (aspirin) (50, 100, 150, 300, 600 mg); monosodium glutamate (1200, 1200, 1200, 1200 mg); sodium metabisulphite dissolved in 100 ml 0.5% citric acid solution (50, 100, 150, 200 mg); artificial colour (30 mg tartrazine, 30 mg erythrosine); sodium nitrate and sodium nitrite (each 25 mg). Two placebos were included: sucrose (5×500 mg) and 0.5% citric acid solution (4×100 ml). All chemicals were packaged in ferric oxide tinted, gelatine capsules, size "0". Seven different sets of the seven chemicals tested were prepared. Since the number of capsules used and the doses varied for the different challenges, the pharmacist ensured that active and placebo substances could not be distinguished by matching the number of capsules. The subject, the physician, the dietitian, and the laboratory assistants were all blinded to the contents of the challenges.

Food chemical challenging was performed under the supervision of a physician. Bronchodilators, adrenaline, and resuscitation equipment were available at all times for the treatment of any acute effects caused by the challenges, which were carried out at least 48 hours apart. Each challenge was administered in divided doses at 15 minute intervals. Each dose was preceded by a spirometric measurement, the first being used to compare all subsequent readings.

The subjects were required to remain under observation for two hours after the final dose of each challenge was taken. If any reduction in FEV_1 or increase in symptoms occurred during the challenge, the subject remained under supervision until the physician was satisfied that symptoms had improved sufficiently and were unlikely to worsen.

ELIMINATION DIET

The elimination diet used is a modification of that developed by Gibson (Swain) and Clancy.[8]

Table 1 Subject details

Subject no.	*Sex*	*Age*	*FEV_1 (% predicted)*	*$PD_{20}FEV_1$ (Mean of run-ins)*	*Medications*
1	F	22	93	0.43	S,B
2	M	48	58	0.33	S,B
3	M	42	119	5.55	S
4	F	40	99	0.08	S
5	F	31	75	0.23	S,B,I,C
6	F	50	58	2.45	S,B,I,C
7	F	51	78	5.93	S,B,I
8	M	35	97	1.67	S,B,F
9	F	21	102	0.38	S,B,I,T
10	F	42	91	0.58	S,B,C
11	F	38	71	0.14	S,B
Mean		38.2	85.6	0.66	
Range		21–51	58–119	0.08–5.93	

FEV_1 = forced expiratory volume in one second; $PD_{20}FEV_1$ = dose of histamine causing a 20% fall in FEV_1 compared with baseline reading; S = salbutamol; B = beclomethasone dipropionate; I = ipratropium bromide; C = sodium cromoglycate; T = theophylline; F = fenoterol.

Table 2 Unmodified diet method challenge results

Subject no.	*MBS*	*ASA*	*MSG*	*Nitrate/ nitrite*	*Food colour*	*Citric acid*	*Sucrose*
1	–10	+ BR/–10	–	+ BR/–10	–	–	–10
2	–10	+ BR	–	–	–	–	+ BR
3	–	–10	–	–	–	–	–
4	–10	–	–	–	–	–	–
5	–10	–10	–	–	+ BR	–	–
6	–	–	–	+ BR	+ BR	+ BR	–
7	–	+ BR	+ BR	+ BR/–10	+ BR	+ BR/–10	+ BR
8	–10	–	–	–	–	–10	–
9	+ BR/–10	–	–	–	–10	–	+ BR
10	–	–	–	+ BR	–	–	–
11	–	–10	+ BR/-10	–	+ BR	+ BR/–10	–

MBS = metabisulphite; ASA = acetyl salicylic acid; MSG = monosodium glutamate; –10 = reduction in forced expiratory volume in one second of ≥ 10%; + BR = an increase in bronchial responsiveness equivalent to ≥ one doubling dose of histamine; – = no response.

It was based initially on the elimination diets of Rowe,[9] Shelley,[10] Feingold,[11] and Warin and Smith,[12] and subsequently on systematic laboratory analysis of the natural salicylate content of a wide range of common foods.[13] The diet excludes all artificial food colours, preservatives, and monosodium glutamate as well as high levels of naturally occurring biogenic amines, salicylates, and free glutamate.

Non-steroidal anti-inflammatory drugs were avoided and those subjects who experienced headaches or other minor pain during the study took uncoloured paracetamol, codeine, or ergotamine compounds where indicated. The diet is known to be low in vitamin C and vitamin A so subjects took a daily multivitamin (Elevit RDI, Roche) which contained no artificial colourings, flavourings, or herbal extracts. No herbal or other vitamin preparations were permitted.

Subjects were required to keep a diary of all food and drinks consumed during the period of the elimination diet.

Table 3 Comparison of unmodified diet with elimination diet method challenge results

Subject no.	*MBS*	*ASA*	*MSG*	*Nitrate/ nitrite*	*Food colour*	*Citric acid*	*Sucrose*
1	Ed	Nd	–	Nd	–	–	–
2	Ed	Nd	–	–	–	–	Nd
3	Ed	Ed/Excl	–	–	–	–	–
4	Ed	–	–	–	–	–	–
5	Ed/Excl	–	–	–	Nd	–	–
6	Ed	–	Ed	Nd	Nd/Ed	Nd	–
7	–	Nd	Nd	Nd	Nd	Nd	Nd
8	–	–	–	–	–	–	–
9	Nd/Ed	–	–	–	–	–	Nd
10	–	–	–	Nd	–	–	–
11	Ed	–	Nd	–	Nd	Nd	–

MBS = metabisulphite; ASA = acetyl salicylic acid;
MSG = monosodium glutamate; Ed = positive response during elimination diet method challenges as measured by a ≥ 20% fall in forced expiratory volume in one second;
Nd = positive response during unmodified diet (no diet) method challenges as measured by a an increase in bronchial responsiveness equivalent to ≥ one doubling dose of histamine; Nd/Ed = positive response in both unmodified diet and elimination diet method challenges; Excl = challenge excluded from results; – = no response.

LUNG FUNCTION MEASUREMENTS

Spirometric function was measured on a Vitalograph spirometer with the subject standing. Forced vital capacity (FVC) and FEV_1 were recorded. Forced expiratory manoeuvres were repeated until two values for FEV_1 repeatable to within 100 ml were obtained and the highest of these two values was recorded.

Bronchial responsiveness was assessed by a histamine inhalation test using the rapid method.[14] The dose of histamine causing a 20% fall in FEV_1 ($PD_{20}FEV_1$) was used to assess bronchial responsiveness and severity of asthma.

DATA ANALYSIS

An increase in bronchial responsiveness following a food chemical of more than or equal to one doubling dose of histamine was regarded as clinically significant. A 20% or greater fall in FEV_1 was regarded as a positive reaction to food chemical challenge. Comparison of the results was performed using sensitivity and specificity analysis.

Food diaries were examined for dietary compliance.

Results

Details of all subjects including their initial $PD_{20}FEV_1$ readings are presented in table 1.

CHALLENGE REACTIONS ON AN UNMODIFIED DIET

Of the 77 food chemical challenges performed on 11 subjects when the diet was unmodified, 20 were followed by an increase in bronchial responsiveness to histamine (table 2). Six of these apparent positive responses were following a placebo challenge.

On seven occasions the increase in bronchial responsiveness was accompanied by a fall in FEV_1 of 10% or more. In 13 of the 77 challenges not all doses were taken due to a fall in FEV_1 of 10% or more (table 2).

In two subjects (subjects 3 and 5 for aspirin and metabisulphite, respectively) FEV_1 fell by more than 20% 90 minutes after the last dose was taken. These two subjects were treated with nebulised salbutamol and therefore could not undergo a histamine inhalation test.

CHALLENGE REACTIONS ON THE ELIMINATION DIET

After one month on the elimination diet, food chemical challenge caused a 20% fall in FEV_1 on 11 occasions in eight subjects – eight to sodium metabisulphite, one to aspirin, one to monosodium glutamate, and one to artificial colour (table 3). There were no placebo responses.

COMPARISON OF ASSESSMENT METHODS

Of the 20 occasions on which an increase in bronchial responsiveness was recorded following the unmodified diet challenges, only two coincided with a positive challenge on the elimination diet (table 3). The results of the challenges in subjects 3 and 5 for aspirin and

Table 4 Sensitivity and specificity analysis

	Positive diet	*Negative diet*	*Total*
Positive histamine	2	18	20
Negative histamine	7	48	55
Total	9	66	75
Sensitivity	2/9 (22%)		
Specificity	48/66 (73%)		
PPV	2/20 (10%)		

PPV = predictive value of a positive result.

sodium metabisulphite, respectively, were excluded from the analysis since comparison between the two methods could not be made. This gave the unmodified diet method a sensitivity of 22%, a specificity of 73%, and a positive predictive value of 10% compared with the elimination diet method (table 4).

Discussion

The sensitivity of challenge testing on an unmodified diet was poor in that only 22% of the positive reactions as assessed by this method were also positive according to the elimination diet method. The predictive value was also poor in that only 10% of the positive reactions as assessed by the elimination diet method would be detected by the unmodified diet method. The specificity of 73% appears to be higher but, because intolerance to chemicals is often confined to one or two chemicals in any individual asthmatic subject, most of the tests would be expected to be negative. Thus, a result of 73% detection of negative reactions is actually quite low.

The cut off point of more than one doubling dose of histamine for a significant change in bronchial responsiveness was chosen because any less than this would be well within the range of normal within subject variation. Calculation of the within subject repeatability according to the method of Peat *et al*[15] and Bland and Altman[16] gave a value of ± 1.33 doubling doses. If the cut off point was increased to 1.5 or even two doubling doses the specificity would increase, but the sensitivity and positive predictive value would reduce to zero. Since sensitivity and the positive predictive value are the most important values, making the criterion for a positive histamine challenge more stringent would worsen the outcome.

In most instances all doses of the food chemicals were taken. On eight occasions the dose administered was lower in the unmodified diet phase and on six occasions the dose was higher (data not shown). Most of the occasions on which the dose administered was lower whilst the subject was on a normal diet were probably due to our criterion of stopping the challenge if spirometric function dropped by 10%. This variability is normal and is not necessarily indicative of a reaction. Metabisulphite was responsible for all of the six occasions when the dose required to elicit a response was lower in the elimination diet phase. This suggests that the elimination diet increases the sensitivity of these individuals to metabisulphite.

There are a number of possible confounding factors which may influence interpretation of test results. Firstly, 90 minutes may not be the most appropriate period of time to measure changes in bronchial responsiveness. This time period was chosen because of the work of Wilson *et al* which showed initially that bronchial responsiveness was significantly increased 30 minutes after ingestion of cola drinks in 10 asthmatic children[4] and later that increases in bronchial responsiveness were even greater 90 minutes after ingestion of ice.[6] Similarly, Hariparsad *et al* studied 10 children with a history of cough or wheeze after drinks coloured with the artificial food colour tartrazine and found that four children had enhanced bronchial responsiveness when tested 30–60 minutes after ingestion of 1 mg tartrazine.[5] In our study one subject who had previously reported a subjective increase in symptoms of asthma the day after a glass of wine had a significantly lower $PD_{20}FEV_1$ reading the morning after consuming a glass of wine. When challenged with metabisulphite (the most likely cause of her symptoms after drinking the wine) 90 minutes after the last dose was taken, she had no change in $PD_{20}FEV_1$ but, later in the day, she reported an increase in wheezing and her Airflometer (Glaxo, Australia) readings taken at home had fallen significantly. The Airflometer provides an integration of rate and flow and readings have been shown to correlate well with FEV_1.[17] It is therefore possible that, if increases in histamine responsiveness do occur after food chemical challenge, the time lag may be greater than 90 minutes in some individuals.

Secondly, if we assume that bronchial responsiveness does increase on exposure to food chemicals, it is possible that foods consumed immediately before commencing challenges whilst on an unmodified diet could also increase bronchial responsiveness. Although this would explain the placebo responses, it means that an elimination diet would be required to avoid false positive results which then defeats the purpose of the abbreviated method. However, it is unlikely that this is the case because all positive reactions as assessed by the elimination diet method would be expected to have had a corresponding increase in bronchial responsiveness to histamine by the unmodified diet method, and this did not occur.

Thirdly, it may be that repeated exposure to the food chemicals is necessary to increase bronchial hyperresponsiveness. Children in the studies conducted by Wilson *et al* and Hariparsad *et al* were not restricted in their dietary intake and may well have been having regular doses of the foods with which they were tested. However, our experience with food sensitive asthmatic subjects has shown that the elimination diet and challenge procedure produces results which are confirmed by long term avoidance of the relevant substances.[7] Since only two challenges produced a positive response in both methods and six of the apparent positive responses on an unmodified diet were to placebos, it is doubtful that the

increase in bronchial responsiveness following challenges using the unmodified diet method was relevant to the true sensitivities of these subjects.

Finally, it is possible that each food chemical behaves differently and that only some food chemicals cause an increase in bronchial responsiveness. Our results show that ingested metabisulphite does not increase bronchial responsiveness in the short term. Due to the small number of subjects sensitive to chemicals other than metabisulphite, it is not possible to say with certainty that these other chemicals do not increase bronchial responsiveness.

This was a very small and highly selected group of asthmatic subjects and was not representative of the asthmatic population. However, since our subjects were selected for the likelihood of food sensitivity, confirmed by the test results, it is reasonable to assume that if there was, indeed, a consistent effect on bronchial responsiveness after challenge with food chemicals, it should be apparent in this group.

We have shown that the results obtained from challenging asthmatic subjects with food chemicals when on a normal diet, using changes in bronchial responsiveness to histamine to detect a positive response, do not correspond to positive responses to food chemical challenges as assessed by significant reductions in FEV_1 whilst on an elimination diet. We conclude that the method of strict elimination diet prior to food chemical challenges, and a 20% reduction in FEV_1 following a challenge, remains the most reliable method for the detection of sensitivity to food chemicals in asthmatic subjects.

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