

Hazards of challenge tests in atopic dermatitis

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It is sometimes desirable to perform challenges with foods or food additives in children with atopic dermatitis (AD). Such challenges can be open, single-blind, or double-blind. The need for this time-consuming and unwieldy procedure is partly attributable to the lack of any other reliable clinical or laboratory test. The failure to develop a simple test can be ascribed to the numerous immunological and pharmacological mechanisms which operate in food or additive intolerance. Some sort of test is required chiefly because parents' observations about food intolerance are notoriously unreliable (1-3).

Challenge tests are fraught with difficulties, but perhaps the most serious hazard is that the procedure may arrive at the wrong answer, leading to the inappropriate inclusion or exclusion of an item from the child's diet. Possible hazards are briefly described below, with attention given to the final one which has caused us particular problems-anaphylactic shock (4).

Nature of food being tested

Difficulties arise if a cooked food is used for testing and the patient is only sensitive to a raw food (5, 6), or vice versa. Cooking has been shown to reduce the sensitizing capacity of cow's milk (7), and intolerance to raw but not cooked egg, potato and fish are well-described, although it is rare for these latter foods to be taken raw, and the use of uncooked food items for challenges is likely to produce an excess of positive responses. The simple but time-consuming solution would be to perform all food challenges with both raw and cooked foods.

It is unclear what dosage of different foods is required to exclude food intolerance. The dos-

age used in studies employing encapsulated foods is limited (8), and it is possible that larger quantities of food may cause an adverse reaction when smaller quantities do not. This must apply particularly to instances of food intolerance where a pharmacological mechanism is involved, such as the adverse effects of foods containing vasoactive amines. But it is also known to apply to other foods such as cow's milk. For example, Hill et al. have reported that whereas 8 to 10 g of milk powder (corresponding to 60 to 70 ml of milk) is adequate to provoke a response in some patients with cow's milk protein intolerance, other patients (with late onset symptoms) required up to 10 times this volume of milk daily for more than 48 h before symptoms developed (9).

Double-blind challenges may by-pass important sites

The administration of food or additives in capsules may by-pass the oral mucosa, thus eliminating possible local reactions in the mouth. In practice, patients whose symptoms are exclusively confined to the mouth are unusual, and knowledge of this enables an alternative challenge procedure. In patients who are intolerant to sulphites, it is well known that the administration of sulphites in capsules or directly into the stomach via a nasogastric tube usually fails to provoke an adverse reaction, whereas the oral administration of solution will succeed in doing so (10, 11).

Failure to employ double-blind methodology

Failure to employ double-blind challenges in an area where parental belief may be very strong is

a potential hazard. An open challenge is an open invitation to the overdiagnosis of food intolerance. In the United Kingdom there is no area of parental belief stronger than the association between food additives and bad behavior, but in one series, double-blind challenges with tartrazine and benzoic acid were negative in all 26 children with a clear parental description of adverse reaction (3).

Failure to employ double-blind placebo control

An error common to many studies of food additives in chronic urticaria (eg. Michaelson et al. (12)), rendering them meaningless, was to employ a standard order of challenges, the placebo always preceding the active substance. This, plus the withdrawal of treatment immediately prior to the challenges, was bound to lead to a greater number of adverse reactions to active substances.

The state of the disease in question

In chronic urticaria it is well recognised that intolerance to salicylates is confined to patients with active disease (13, 14). It is highly likely, though unproven, that a similar situation exists in atopic dermatitis. It is a common though poorly documented observation that AD improves and often disappears altogether while a child is abroad on holiday, and while on holiday the child can take with impunity foods which normally provoke worsening of the dermatitis. It is possible that a food challenge performed during a quiescent phase of the disease may fail to provoke an adverse reaction. The converse could also occur; in the "angry back" or "excited skin" syndrome (15), patch tests may produce false positive reactions, although there is no evidence of a similar phenomenon in atopic dermatitis.

Tolerance

The mechanisms whereby children become tolerant or sensitized to foods and food additives

are poorly understood. The regular administration of salicylates to patients with salicylate intolerance quickly leads to a state of tolerance to salicylate (16). The mechanism in this instance, although not fully understood, is probably pharmacological (17). It is likely, although unproven, that a similar phenomenon occurs with certain food additives. Thus a double-blind challenge performed while a patient is regularly consuming a food may fail to provoke an adverse reaction.

Additive effect of multiple intolerance

Where food intolerance exists in children with AD, it is not uncommon for the patient to be intolerant to several foods. In these patients, the removal of only one or two offending items may fail to help the patient. By the same token, it is possible that when most or all offending foods have been removed, the re-introduction of a single offending food may not provoke any detectable worsening of the dermatitis. This phenomenon has *not* been objectively demonstrated but may occur, and could account for a negative food challenge. A related but not identical phenomenon is the patient whose adverse reaction to a food is enhanced or facilitated by the prior ingestion of acetylsalicylic acid (18).

A variation of this problem is where food intolerance is combined with allergy to pets or house dust mites. Although it has never been objectively verified, our own experience is that where pet or house dust mite allergy is a major factor, this may obscure the result of food challenges.

Disease suppressed by topical or systemic steroids

It is unclear whether the enthusiastic and liberal application of topical steroids could mask an adverse reaction to a food. It is a common observation that the majority of adverse reactions to foods in children with AD are of rapid onset and urticarial in nature, and steroids would not be expected to obscure these quick reactions. Whether oral or systemic steroids can obscure delayed reactions to food is unknown.

In practice, steroid treatment seems an unlikely source of confusion.

The child has grown out of his food intolerance

The very short duration of food (19) and additive (20) intolerance, and the natural history of AD, mean that by the time challenges are performed some patients will have become tolerant to items which previously provoked their dermatitis.

Other factors necessary for positive challenge

In a subgroup of patients with exercise-induced anaphylaxis, symptoms only occur if exercise follows the ingestion of a particular food (21, 22). Exercise or the food alone fail to provoke symptoms. Simple double-blind food challenges would fail to provoke an adverse reaction in such patients. This should not be a confounding problem with food challenges in children with atopic dermatitis.

Duration of observation

A brief duration of observation (eg. 4 h) after a challenge will prevent detection of any delayed reactions and thereby may fail to detect trigger substances.

Failure to fully disguise the food being tested

A criticism of the technique of food challenges with encapsulated food is that after the capsule has dissolved in the stomach the patient may eructate and thereby detect foods with characteristic tastes or odors. This may be a problem with adults, but is less likely to be so in children. Some studies stretch credibility, an example being the claim in one study of intolerance to cola drinks (23) that children were unable to distinguish between PepsiCola and saccharin flavored fizzy water.

Statistical mishandling

A frequent error is to forget that a challenge procedure may coincide with worsening of the

dermatitis, so that there is a chance of the wrong inference being drawn from a challenge result. The risk of this happening can be quantified, and the probability of such errors has been discussed recently by Pearson (24).

Anaphylactic shock

It is well recognised that anaphylactic shock can occur in some individuals as a result of the ingestion of certain foods. Food challenges are usually avoided in the face of a history of anaphylactic shock, because of the risk of a severe reaction or even death. However, it is often forgotten that anaphylactic shock is a potential albeit remote hazard of any food challenge, even in a subject who has not previously experienced anaphylactic shock. For example, in Goldman's classic study of cow's milk protein intolerance, anaphylactic shock had been noted prior to cow's milk challenge in 5 children, but another 3 out of 89 children developed anaphylactic shock as a new symptom after cow's milk challenge (25). In recent years, we have become aware that anaphylactic shock represents a significant hazard of food challenges in children with AD who have been treated with an elimination diet (4).

In 1984, we reported 4 children with AD in whom the deliberate reintroduction of a single food caused anaphylactic shock. The foods were soya, chicken, corn and cow's milk. In 2 patients spontaneous recovery occurred, but in 2 others resuscitation and intensive care were required. Since that time we have seen 2 further cases of anaphylactic shock, one following a planned challenge with peas and the other following the inadvertent ingestion of cow's milk protein. These 2 cases are reported below.

CASE REPORTS

Case 1

A child with exceptionally severe atopic dermatitis was referred to us at the age of 2 1/2 years. He was bottle fed with a cow's milk formula,

and solids were introduced into his diet from 4.5 months of age. He suffered from AD from the age of 3.5 months which was resistant to conventional topical treatment, and he had received two courses of oral prednisolone. Recurrent staphylococcal skin infections led to extensive immunological investigations, but there was no evidence of any underlying immunodeficiency disorder. Examination showed widespread and severely inflamed atopic dermatitis. There was a history of immediate scratching and urticaria, followed by loose stools and vomiting after the ingestion of cow's milk, wheat, egg, green beans, cauliflower, pears, lamb and chicken. Pineapple had been noted to cause, in addition to the above, angioedema of the lips.

Because of the history of food intolerance, he was admitted to hospital at the age of 2.5 years, and treated with an elemental diet (Vivonex) for 42 days. The skin lesions improved only slightly on this regimen. In view of the severity of the skin lesions and the fact that severe dermatitis of the auditory meatus had prevented the use of hearing aids for over 6 months, he was treated with intramuscular adrenocorticotrophic hormone (ACTH) 40 units daily. He remained on the elemental diet, and a restricted diet was re-started, excluding foods to which he was known to be intolerant. On day 52 of his admission to hospital he received lunch which included a small number of peas. Within 15 minutes he was noted to be deeply cyanosed, with very poor air entry, hypotension, and generalized urticaria, and for a short time he became unconscious. He was given intramuscular chlorpheniramine and nebulised terbutaline and recovered in minutes, so that 3 hours after ingestion he just had some mild residual urticaria which quickly settled.

Case 2

A boy with severe atopic dermatitis was first seen at Booth Hall Children's Hospital at the age of 4.5 years. He had been breast fed for 4 months, but atopic dermatitis developed at the age of 4 weeks. There was a history that ingestion of cow's milk, chocolate, tomato, and

egg caused urticaria and angioedema, and exposure to cats and dogs had been noted to provoke asthma. Because of this history and the presence of severely inflamed atopic dermatitis he was treated with a trial of an empirical elimination diet, and for 6 weeks he was permitted to consume lamb, potato, apple, carrot and parsnip and no other foodstuff. At the end of 6 weeks only slight improvement was noted, and foods were re-introduced singly without the discovery of any new food triggers. At the age of 5.5 years, by which time his dermatitis had largely resolved, his mother purchased from a "health food" shop some cheese which was alleged by the retailer to be completely milk-free. (Subsequent enquiries revealed that this was a "vegetarian" cheese prepared with rennet of vegetable origin). Consumption of a small amount of this cheese was followed 10 minutes later by severe wheezing, cyanosis and obstructed respiration, and the patient told his mother he was dying and then collapsed. The general practitioner was called and administered an antihistamine (trimeprazine) and a bronchodilator (terbutaline), but although his general condition improved he was admitted to hospital because of persistent severe bronchospasm, which had resolved by the following day after treatment with intravenous hydrocortisone and aminophylline and nebulised terbutaline.

DISCUSSION

Anaphylactic shock comprises a rare but serious potential complication of the use of elimination diets in children with atopic dermatitis. As a result of our experience, we recommend the following strategy for all food challenges in children with atopic dermatitis:

- We warn the parents (and for challenges in hospital we also warn the nursing and medical staff) of the possibility of dangerous reactions.
- For challenges performed outside hospital (which constitute the vast majority) we recommend that the new food is first rubbed on to the skin, and the challenge abandoned if an urticarial reaction is provoked. The absence of an urticarial reaction is no guarantee

that anaphylactic shock will not occur, and most of our patients receive a sedating antihistamine (trimeprazine) nightly which may obscure an urticarial reaction. A further problem with this crude form of skin testing is that it is not uncommon to find patients who are unable to tolerate skin contact with a food but who can ingest the same food with impunity. Nevertheless, we would take an obvious urticarial reaction as an indication for extreme caution.

- For challenges performed outside hospital, we recommend that both parents be present.
- When re-introducing a food for the first time we now recommend that only a minute portion (equivalent to a grain of rice) be given. It is unclear whether there is a rational basis for this strategy, as serious anaphylactic reactions appear to be possible after ingestion of very small quantities of specific foods (26, 27).
- We have not yet supplied parents with pre-loaded syringes of adrenaline for home use.

It is increasingly appreciated that although the major risk for anaphylaxis is in the first few minutes after exposure to an antigen, severe anaphylactic reactions can be delayed (4, 28). In relation to food challenges, it has been suggested that "since severe reactions occur rapidly, the patient should be watched for thirty minutes" (29), but experience with one of our patients suggests that dangerous reactions may be delayed by many hours. There may be a special hazard of delayed anaphylactic reactions to cow's milk protein (30), and it was this which caused delayed anaphylaxis in one of our patients (4). For cow's milk challenges in infants with a history of cow's milk protein intolerance, we perform all challenges in hospital and keep the child under observation for 12 h (30). One option would be to insist on all food challenges being done in hospital, keeping the child under observation for 12 h, but this would be an unrealistic burden for the family and hospital alike. It is important to remember that although the major clinical features of anaphylaxis are angioedema and large airway obstruction, generalised urticaria, bronchospasm and hypotension, the features vary a great deal from case to

case, so that, for example, shock can be a major feature occurring without urticaria (31).

The relatively high incidence of anaphylaxis in our patients has been commented upon, for it is at variance with the observations of some other workers (32). Our comments are:

- From discussions with colleagues, it is clear that there is a general under-reporting of serious episodes of anaphylaxis in childhood due to foods. Our original report mentioned briefly a death occurring during a cow's milk challenge (4), and a recent study was able to report on no less than 7 cases of fatal food-induced anaphylaxis (26).
- Our patients were a highly selected group of children with exceptionally severe and widespread atopic dermatitis, and constitute a special group.
- In 2 of our 6 patients with anaphylaxis, the trigger food was cow's milk, and cow's milk is well-recognised to be an especially potent cause of anaphylaxis following a period of avoidance (25).
- The remaining 4 patients had all received a prolonged period of treatment with an elemental diet, an exceptionally rigorous form of antigen exclusion, and it is quite possible that the use of such elemental diets may carry a special hazard of anaphylaxis, for reasons which are not known. The fact that anaphylaxis has not been a problem in those patients who received a more conventional type of elimination diet also incriminates the use of elemental diets as a contributory factor. However, those who have received this most extreme dietary approach were also the most severely affected patients, and it could be that these constitute an especially vulnerable group.
- None of our patients had been receiving beta-adrenergic agonists, which are well known to potentiate anaphylaxis (33, 34).

It appears that almost any food which is capable of producing an immediate hypersensitivity reaction is potentially capable of causing anaphylactic shock. Foods well-described as triggers of anaphylactic shock or explosive allergic reactions are diverse, and include cow's

milk (25, 35), beans (35), fish (35), rice (35), potato (35), nut (35), tangerine (35), orange (36), soya (4, 37), chicken (4), corn (4), wheat (38), banana (38), kiwi fruit (40), sesame seed (41), sunflower seed (42), millet seed (43), mango (44, 45), chamomile (46) and celery (only raw) (47) or when raw or cooked (48).

Anaphylactic shock is a constant worry when dealing with patients with atopic disease and food intolerance, and it is one of the reasons why unsupervised dietary treatment and unorthodox approaches to allergy treatment (49) are potentially hazardous. Even skin testing, especially intradermal testing, carries the risk of fatal anaphylaxis (50). Fortunately even where reactions are severe it appears that a number of children will grow out of their intolerance (51).

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