

Allergic reactions to oral, surgical and topical bovine collagen

Anaphylactic risk for surgeons

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Abstract

Background: Two cases of allergic (IgE-mediated) reaction to bovine collagen are described. Both patients developed conjunctival oedema in response to the topical application of highly purified bovine collagen to the eye during ophthalmic surgery (corneal shields and catgut suture material). One patient developed periorbital angioedema and angioedema of the throat after the ingestion of bovine collagen in the form of gelatin-containing foods.

Methods: The presence of allergen-specific IgE was evaluated by skin prick testing with collagen-derived products, and by topical challenge with a highly purified bovine collagen-derived corneal shield.

Results: In both patients, application of collagen to the eye reproduced the original subconjunctival oedema. In one patient, skin testing with purified and crude extracts of bovine collagen in the form

of a corneal shield, catgut suture material and edible gelatin demonstrated evidence of collagen-specific IgE.

Conclusions: Clinical reactions to collagen are rare. Nevertheless, patients with a history of allergic reactions to bovine collagen-derived products should be investigated because of the widespread use of collagen-derived therapeutic devices, the potential for immunological cross-reactivity with dietary collagen (gelatin) and the potential for anaphylaxis.

Key words: Allergy, collagen, sutures, corneal shields, gelatin, urticaria.

Allergy ('immediate hypersensitivity') is defined as the development of IgE-mediated inflammatory reactions to exogenous proteins (allergens), whether they be inhaled, ingested or applied topically. This can occur only after prior exposure

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to allergen. Up to 25% of the population will develop clinical manifestations of allergic disease during their lifetime, most commonly to inhaled allergens derived from grass pollens or dust mites, but less often due to foods. The production of allergen-specific IgE results in the 'arming' of mast cells present within the skin, respiratory tree, gut and eye. Re-exposure to the same allergen induces mast cell degranulation and the release of vasoactive mediators including histamine, leading to localised pruritus, erythema and oedema, typically over a period of 10 to 30 minutes. Anaphylaxis may occur in patients with exquisite sensitivity. The presence of allergen-specific IgE may be evaluated by skin testing, which involves the introduction of small amounts of allergen into the dermis by pricking the skin through a drop of allergen extract.

Immune reactions to drugs and therapeutic devices may also occur. Allergic reactions are the most common, and account for approximately 25% of adverse reactions to medication.¹ Hypersensitivity to such diverse agents as antibiotics, narcotics, anaesthetic agents, radiographic contrast agents, topical chlorhexidine, dextran-containing colloids as well as to latex-derived proteins, have been described. Reports of adverse reactions to bovine collagen, however, have been restricted to descriptions of localised redness and swelling following plastic surgery using collagen implants and descriptions of wound breakdown with the use of 'catgut' suture material.^{2,3} Two recent cases demonstrate a convergence between allergic reactions to collagen as a therapeutic device, and in its edible form as gelatin.

Case 1

A 39-year-old woman presented with a 16-year history of episodic urticaria. The first occurred at the age of 23 years when she developed angioedema of her throat and around her eyes, attributed at that time to ingestion of marshmallows. She remained well until the age of 37, when

she developed a periocular angioedema which resolved spontaneously over a period of four hours. In the month before presentation, she had experienced a total of four similar episodes, one of which clearly followed ingestion of marshmallows two hours earlier. Review of her past history revealed surgery to the left eye at the age of three years and 23 years to correct congenital strabismus. On both occasions, pruritus and swelling of the left eye occurred within two hours of the operation; catgut sutures were used during both procedures. She had not undergone other surgical procedures. She had no significant previous occupational or recreational exposure to animals. In the absence of a commercial extract for skin testing, a slurry of marshmallows in sterile saline (10 weight/volume) was prepared. Skin testing resulted in a 1 cm welt with surrounding flare, isolated to the gelatin component of marshmallows with further testing. Subsequent skin testing with crude extracts of purified gelatin (boiled in water and allowed to cool and set), catgut suture material, a Surgilens corneal shield, edible jelly and jelly beans all induced similar weals with surrounding flares. (Non-specific irritation by these crude extracts was excluded by parallel testing of a control subject). Negative skin tests were observed with saline controls and with potential minor sources of dietary collagen such as crude preparations of beef, veal, chicken and pork. Application of a new Surgilens corneal shield to the patient's left eye induced irritation, erythema and subconjunctival oedema visible on slit lamp examination within 20 minutes (Figure 1). Three weeks after appropriate dietetic advice regarding gelatin avoidance, another episode of periocular urticaria occurred within two hours of ingestion of a gelatin-containing ice-confection.

Case 2

A 62-year-old woman was admitted for elective cataract surgery. At the end of the procedure, topical solutions of gentamicin and prednisolone



Figure 1 Application of a bovine collagen-derived Surgilens to the left eye of Case 1 resulted in irritation, redness and subconjunctival oedema within 20 minutes.

sodium phosphate were applied under the occlusion of a bovine collagen-derived corneal shield (Surgilens, Chiron Ophthalmic, Irvine, California). Within 30 minutes she developed pain and oedema of the left tarsal and bulbar conjunctiva, which resolved spontaneously within three hours of removal of the lens. Subsequent separate rechallenge with solutions of gentamycin or prednisolone applied to the left eye failed to reproduce the swelling. Rechallenge with a new corneal shield (after hydration in saline) resulted in almost instant itch and irritation, followed by oedema of the tarsal and bulbar conjunctiva within 20 minutes. Further questioning revealed no past history of allergic reactions to drugs or food, although she had worked with small animals (not cattle) as a research assistant. She declined further investigation at that time but agreed to skin testing a year later with crude preparations of gelatin, catgut suture material and the Surgilens corneal shield. All skin tests were negative in the presence of an appropriate positive (histamine) and negative control. In view of previous discomfort on two occasions with application of the corneal shield, rechallenge was declined.

Discussion

The intestines of sheep or cattle have been the prime source of strings for musical instruments since the Middle Ages, and subsequently in the production of suture material, after appropriate processing to sterilise and inhibit physiological breakdown. Other forms of collagen are extracted from the bone and skin of cattle (the main source in Australia) or pigs. Unlike collagen, gelatin is not found in nature, but is extracted by acid and alkaline hydrolysis, followed by heating to temperatures up to 90° Celsius. Gelatin has a variety of therapeutic uses, including the collagen implants of plastic surgery, gelatin sponges used for surgical haemostasis, in some therapeutic contact lenses, in colloid solutions for intravenous administration, as a stabilising agent in some vaccines and as a binding and coating agent in tablets and capsules. It is also used in photographic emulsions, glues, matches, cosmetics, shampoos and is ubiquitous in processed foods including confectionery, food thickeners, dips, glazes, icing, soups, chilled dairy products (e.g., yogurt, mayonaise, mousse, icecream, cheeses), in smallgoods (e.g., sausage coatings, salami, tinned hams, pate) and for the clarification of fruit juices and wine.

The safety of collagen is reflected in the relative paucity of reports of allergic reactions to gelatin. Indeed, the United States Food and Drug Administration classifies gelatin as 'generally regarded as safe' for human consumption. This is not a cause for complacency. Anaphylaxis has been reported in response to gelatin-containing colloids,⁴ to the gelatin component of some vaccines,⁵ and gelatin has been associated with postoperative fever and eosinophilia following the use of a haemostatic microfibrillar collagen sponge.⁶

In both cases reported here, allergic responses were observed following the topical application of highly purified bovine collagen, consistent

with collagenous material (rather than a contaminant) being the target of the immune response.

Interestingly, loss of reactivity over a 12-month period was observed in the second patient, although precedents for this exist in the literature with regard to antibiotic allergy.⁷ In the first patient, however, urticaria and angioedema occurred with oral ingestion as well, something which clearly followed the first reaction to topical collagen (suture material) by many years. The clinical and skin test cross-reactivity between collagen and gelatin in this patient means that the target of the immune response is resistant to hydrolysis and is stable at high temperatures, although the helical structure of collagen re-forms as gelatin is cooled. Since the development of allergy requires prior exposure to allergen, it is interesting to speculate whether it was exposure to topical collagen or dietary gelatin which resulted in the development of hypersensitivity in these patients.

With the widespread use of collagen-containing therapeutic devices, it is essential to investigate the patient presenting with a history of possible adverse reactions to this material, particularly in view of the immunological cross-

reactivity between its various forms and the potential for anaphylaxis.

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