

Notable Cases

Echinacea-associated anaphylaxis

Raymond J Mullins

A woman with atopy experienced anaphylaxis after taking, among other dietary supplements, a commercial extract of echinacea. Hypersensitivity was confirmed by skinprick and RAST testing. Regular ingestion of echinacea by up to 5% of surveyed patients with atopy, combined with detection of echinacea-binding IgE in atopic subjects (19% by skin testing; 20% with moderate to strong reactivity by RAST testing), raises the possibility of severe allergic reactions, even with first-time use, due to cross-reactivity with other structurally similar allergens. Patients with atopy should be cautioned about the risk of developing life-threatening reactions to complementary medicines, including echinacea. (MJA 1998; 168: 170-171)

Up to a quarter of the population will develop an allergic reaction during their lifetime, most commonly to inhaled allergens derived from grass pollens or dust mites. Atopic individuals have a greater risk of developing more frequent or severe allergic reactions.^{1,2} Despite the common perception that “natural therapy” or “herbal remedies” are relatively safe, toxic and hypersensitivity reactions have been described.³ Recent reports have highlighted the risk of potentially life-threatening reactions to dietary supplements, such as royal jelly, in patients with atopy.⁴

Echinacea, a flowering plant (coneflower), and a member of the daisy family, is one popular dietary supplement. Extracts of echinacea are available as capsules, liquid or in a dried form for infusion. Extracts of the flower, root or whole plant have been promoted as enhancing general well-being and resistance to infection or as a treatment for allergic disease. Here I describe a case of anaphylaxis after echinacea ingestion.

Clinical record

A 37-year-old woman had been in the habit of taking dietary supplements for “prophylaxis” on an irregular basis (including echinacea) for two to three years. At 0730 one morning, over a period of about 5 to 10 minutes, she ingested vitamins B₁₂ and E, a herbal iron preparation (FeFol), folate, vitamin B complex, a multivitamin capsule, zinc, antioxidants, a garlic and onion preparation, and evening primrose oil.

At about 0745, the patient swallowed 5 mL (approximately double the manufacturer’s recommended amount) of a commercially prepared 40% alcohol in water solution of echinacea, further diluted in apple and blackcurrant juice (according to the manufacturer’s label). The amount ingested was equivalent to 3825 mg whole plant extract of *Echinacea angustifolia* and 150 mg dry root of *E. purpurea*. She experienced an unusual (for her) immediate burning of the mouth and throat. Tightness in the chest, generalised urticaria and diarrhoea developed by 0800, within a few minutes of eating a mouthful or two of rice cereal and soy milk. The patient was transported to hospital by ambulance after self-administering 75 mg of promethazine orally. The patient was observed in the

emergency department for two hours. Her symptoms resolved completely without the need for further treatment.

Her intercurrent problems included mild wheezing precipitated by infection, allergic rhinitis and oral pruritus caused by various raw (but not cooked) fruit and vegetables, known as “oral allergy syndrome”⁵ (although apple and blackcurrant juice did not cause symptoms). She was also allergic to banana, with accidental exposures in the past resulting in urticaria and/or angioedema. She had taken echinacea intermittently since the early 1990s, most recently within a couple of weeks and from the same bottle, without the symptoms described above. Physical findings were unremarkable.

About two weeks later, after referral by the patient’s general practitioner for investigation of anaphylaxis, I performed skinprick testing using commercially available glycerinated allergen extracts (10% weight/volume; Bayer Australia, Sydney). Positive wheals were observed to house dust mite (*Dermatophagoides pteronyssinus*; 10 mm), cat epithelium (5 mm), perennial ryegrass (*Lolium perenne*; 10 mm), canary grass (*Phalaris canariensis*; 8 mm), birch tree pollen (*Betula* sp; 10 mm) and *Alternaria tenuis* mould (3 mm). Histamine (10 mg/mL) and 50% glycerine/saline were used as positive (5 mm) and negative (0 mm) controls, respectively. Skinprick testing with the aqueous echinacea solution ingested gave a 3 mm flare alone, whereas a glycerinated extract from the same manufacturer (which she had also ingested in the past) resulted in a 3 mm wheal and 5 mm surrounding flare. Similar results were obtained with intradermal testing of the same extracts diluted in sterile saline, with demonstrable wheals at concentrations of 1:100 and 1:10 000, respectively.

Negative reactions were observed to commercial extracts of rice and soy protein, the fruit juice in which the echinacea was diluted, as well as crude extracts of the other dietary supplements (10% weight/volume in sterile saline). Non-specific skin irritation by these extracts was excluded by parallel skin testing of a control subject. A diagnosis of possible echinacea-induced anaphylaxis was made. Radioallergosorbent (RAST) testing of the patient’s serum confirmed the presence of echinacea-binding IgE by a previously described method.⁶

Further investigations

Because no references to echinacea-associated anaphylaxis could be found in the English scientific literature, sensitivity to echinacea was assessed in new patients referred for investigation of asthma or allergic rhinitis. Skinprick testing of 84 consecutive patients with asthma or allergic rhinitis demon-

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strated reactivity to the same aqueous or glycerinated extracts of echinacea in 16 subjects (19%); only two had ever ingested echinacea. Almost all subjects had strong reactivity to grass pollens on skin testing (94%), compared with reactivity to dust mite (56%), alternaria mould (40%), birch pollen (3%) or cat epithelium (19%).

An audit of files from 600 patients with atopy (200 from the same period each year from 1995 to 1997) showed that patient-reported use of dietary supplements (and echinacea-derived extracts) rose from 7.5% (nil) in 1995, to 17% (5%) and 25% (3%), respectively, in the following two years.

Echinacea-binding IgE (by RAST testing) was found in 11 of 15 randomly selected stored sera from patients with atopy (eight weak positives, two moderate positives, one strong positive — ie, 20% moderate to strong reactivity; Dr Brian Baldo, Senior Scientist, Kolling Institute for Medical Research, Sydney, personal communication).

Discussion

Extracts of *Echinacea angustifolia* (and its close relative *E. purpurea*) were originally used by Native Americans as antiseptics and for the treatment of wounds and infection.⁶ Widespread use, particularly to enhance resistance against infection, is largely based on in-vitro studies showing immunomodulatory effects. Plant-derived polysaccharides are thought to be responsible for many of echinacea's purported properties, with minor constituents such as inulin, alkaloids and caffeic acid esters being potentially bioactive as well. Activation of natural killer cells and macrophages, inhibition of hyaluronidase, increased production of cytokines (interleukin-1, tumour necrosis factor) and oxygen free radicals, and anti-inflammatory properties have all been described.⁷⁻⁹

While non-IgE-mediated (anaphylactoid) reactions to one of the other ingested dietary supplements cannot be totally excluded in this patient, this seems unlikely given the patient's immediate pharyngeal irritation with echinacea, the positive skinprick and RAST test results, and the difficulty in conceiving that the other supplements could have triggered direct mast cell degranulation by any known non-IgE-mediated mechanism.¹⁰

Although echinacea challenge was ruled out on ethical grounds, rechallenge with all the other supplements taken by the patient would strengthen the case that these substances did not contribute to the reaction. The patient, however, declined such a rechallenge.

There have also been other reports of adverse reactions associated with echinacea. For example, 11 reports involving echinacea were made to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) between July 1996 and September 1997, including three reports each of suspected hepatitis or asthma, one report each of unspecified rash, rash/myalgia/nausea, urticaria, anaphylaxis (this case), and another of dizziness and tongue swelling. Echinacea was the only substance reported in five of the eight cases suggestive of hypersensitivity, with onset of symptoms identifiable within 24 hours of ingestion in two reports (Dr Patrick Purcell, Acting Secretary, ADRAC, personal communication). Furthermore, there are additional published reports of echinacea-related contact dermatitis and anaphylaxis.^{11,12}

The audit findings of increasing use of dietary supplements confirm recent Australian data in which up to 50% of people

surveyed reported using some form of alternative medicine (apart from vitamins) in the preceding 12 months, mainly for reasons of enhanced well-being rather than for the treatment of illness.^{13,14} That large numbers of atopic patients routinely ingest dietary supplements is of particular concern, as toxic, allergic and idiosyncratic reactions have been associated with their use.^{3,4}

The presence of positive RAST and skin tests to echinacea in asymptomatic atopic subjects (most of whom had never ingested the plant) raises the possibility of cross-reactivity between structurally related proteins common to echinacea, aeroallergens of diverse nature,¹⁵ and perhaps even foods. Precedents for cross-reactivity between ingested and inhaled allergens include (i) oral pruritus or anaphylaxis triggered by fresh fruit in some patients with grass pollen allergy ("oral allergy syndrome"),⁵ (ii) possible cross-reactivity between royal jelly and aeroallergens,¹⁶ and (iii) proposals that tropomyosin may be a common allergen in patients with crustacean and inhaled insect allergy.¹⁷ If this cross-reactivity occurs, then patients with atopy may be at particular risk of developing life-threatening reactions to complementary medicines with even their first exposure, and they should be cautioned appropriately about their use.

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References

1. van Asperen PP, Kemp AS, Mellis CM. A prospective study of the clinical manifestations of atopic disease in infancy. *Acta Paediatr Scand* 1984; 73: 80-85.
2. Adkinson NF Jr. Risk factors for drug allergy. *J Allergy Clin Immunol* 1984; 74: 567-572.
3. Drew AK, Myers SP. Safety issues in herbal medicine: implications for the health professions. *Med J Aust* 1997; 166: 538-541.
4. Leung R, Thien FCK, Baldo B, Czarny D. Royal jelly-induced asthma and anaphylaxis: clinical characteristics and immunological correlations. *J Allergy Clin Immunol* 1995; 96: 1004-1007.
5. Ortolani C, Ispano M, Pastorello E, et al. The oral allergy syndrome. *Ann Allergy Asthma Immunol* 1988; 61: 47-52.
6. Bisset NG, editor. Herbal drugs and phytopharmaceuticals. Stuttgart: Medpharm Scientific Publishers, 1994: 182-184.
7. Stimpel M, Proksch A, Wagner H, Lohmann-Matthes ML. Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fraction from the plant *Echinacea purpurea*. *Infect Immun* 1984; 46: 845-849.
8. Roesler J, Emmendorffer A, Steinmuller C, et al. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocytic system. *Int J Immunopharmacol* 1991; 13: 931-941.
9. Tubaro A, Traghi E, Del Negro P, et al. Anti-inflammatory activity of a polysaccharidic fraction of *Echinacea angustifolia*. *J Pharm Pharmacol* 1987; 39: 567-569.
10. Lane SJ, Lee TH. Anaphylaxis. In: Kay AB, editor. Allergy and allergic diseases. Oxford: Blackwell Science, 1997: 1550-1572.
11. Bruynzeel DP, Van Ketel WG, Young E, et al. Contact sensitisation by alternative topical medicaments containing plant extracts. *Contact Dermatitis* 1992; 27: 278-279.
12. *Immuna allergische Reaktionen nach Echinacea-Extrakten (Echinacin, Esberitox N u.a.)*. *Arznei-Telegramm* 1991; 4: 39.
13. MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996; 347: 569-573.
14. Kristoffersen SS, Atkin PA, Shenfield GM. Uptake of alternative medicine. *Lancet* 1996; 347: 972.
15. Pham NH, Baldo BA, Bass DJ. Cypress pollen allergy. Identification of allergens and cross-reactivity between divergent species. *Clin Exp Allergy* 1994; 24: 558-565.
16. Baldo BA. Allergies to wheat, yeast and royal jelly: a connection between ingestion and inhalation? *Monogr Allergy* 1996; 32: 84-91.
17. Leung PSC, Chow WK, Duffey S, et al. IgE reactivity against a cross-reactive allergen in crustacea and mollusca: evidence for tropomyosin as the common allergen. *J Allergy Clin Immunol* 1996; 98: 954-961.

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