Adverse reactions associated with echinacea: the Australian experience

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Background: Fifty percent of Australians use complementary and alternative medicines (other than vitamins) in any 12-month period, of which echinacea-containing products are increasingly popular. Recent reports have highlighted the risk of allergic reactions to complementary medicines in atopic patients.

Objective: To determine the characteristics of adverse reactions linked to use of the popular herbal remedy echinacea.

Methods: Five privately referred patients were evaluated by the authors in their office practice via skin prick testing (SPT) on the volar aspect of the forearm and radioallergosorbent test after adverse reactions to echinacea. As there was little published information on adverse reactions to echinacea, reports to the Australian Adverse Drug Reactions Advisory Committee were reviewed. Those suggestive of possible allergic reactions were evaluated in greater detail by anonymously surveying the healthcare professionals who had reported the cases and from one unreported case. Serum was collected for further analysis where possible.

Results: Five cases of adverse reactions to echinacea were personally evaluated by the authors. Two patients suffered anaphylaxis and a third had an acute asthma attack 10 minutes after their first ever dose of echinacea. The fourth patient suffered recurrent episodes of mild asthma each time echinacea was ingested, and the fifth developed a maculopapular rash within 2 days of ingestion which recurred when rechallenged. Three of the patients had positive SPT results. Three reported repeated spontaneous "challenges" and symptoms after further ingestion of echinacea. Fifty-one Australian adverse drug reports implicating echinacea were also reviewed. There were 26 cases suggestive of possible immunoglobulin E-mediated hypersensitivity (4 anaphylaxis, 12 acute asthma, 10 urticaria/angioedema). Of these 26 patients, age ranged from 2 to 58 years, 78% were female and >50% were known to be atopic. Four were hospitalized, 4 reacted after their first known exposure, and 1 patient suffered multiple progressive systemic reactions. Twenty percent of 100 atopic subjects who had never taken echinacea also had positive SPT results to this substance when tested by one of the authors in his office practice.

Conclusion: Some atopic subjects have positive SPT results to echinacea in the absence of known exposure. Atopic subjects are also overrepresented in those experiencing reactions to echinacea. The possibility that cross-reactivity between echinacea and other environmental allergens may trigger allergic reactions in "echinacea-naïve" subjects is supported by the Australian data. Given its widespread (and largely unsupervised) community use, even rare adverse events become inevitable. Atopic patients should be cautioned appropriately.

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INTRODUCTION

Despite the common perception that "natural therapy" is safe, toxic and hypersensitivity reactions to complementary and alternative medicine (CAM) have been described.[1–4] Atopic individuals seem to be at particular risk of allergic reactions.[5,6] This is of particular concern, given that atopic patients are increasingly using these medicines for treatment of their allergies.[7] Recent reports have highlighted the risk of allergic reactions to herbal remedies such as royal jelly in asthmatic patients,[8–10] and more recently, echinacea.[11,12]

Echinacea (or coneflower) is a flowering member of the Asteraceae (Compositae) family whose other members include *Ambrosia* (ragweed) species, *Artemisia* (mugwort, sagebrush) species, as well as chrysanthemums, dahlias, sunflowers, marigolds, and daisies.[13] The plant is native to the United States. Large-scale cultivation combined with increasing popularity and community awareness in Australia and the United States has led to widespread use.[14]

Extracts of *Echinacea angustifolia* (and its close relative *Echinacea purpurea*) were originally used by Native Americans as antiseptics and for the treatment of wounds and infection.[15] This is reflected it its contemporary use to enhance resistance against infection, although some practitioners have advised its use for treatment of other conditions including allergy.[16] Extracts of the flower, root, or whole plant are available as capsules, tablets, liquid, or in a dried form for infusion.

Plant-derived polysaccharides are thought to be responsible for many of echinacea's in vitro immunomodulatory properties. Minor constituents such as inulin, alkaloids, and caffeic acid esters seem to be bioactive as well. Echinacea is not in itself viricidal or bactericidal. Rather, activation of natural killer cells and macrophages, inhibition of hyaluronidase, increased production of cytokines (interleukin 1, tumor necrosis factor), and oxygen free radicals, and anti-inflammatory effects are thought to be responsible for its purported properties.[17–21] Despite evidence of in vitro immunomodulatory activity, the results of human studies are either conflicting or

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open to interpretation, largely related to trial size and design.[22–27]

METHODS

Adverse reactions to echinacea were observed by the authors in five patients referred for evaluation by their general practitioner. Skin prick testing (SPT) was performed in the authors' practice using commercially available glycerinated allergen extracts and histamine acid phosphate 10 mg/mL as the positive control, as previously described[11] (Bayer Australia, Sydney, Australia) and using a commercially available glycerinated extract of echinacea purchased by RJM. This extract had been shown to contain echinacea (Dr. Patrick Purcell, Therapeutic Goods Administration [TGA], Australian Commonwealth Department of Health, personal communication, 1998). SPT was performed on the volar aspect of the forearm using metal lancets (Miles Allergy Products/Hollister Stier, Spokane WA), puncturing the skin at an angle of 45° to 60° to the skin surface. Allergen extracts were spaced no closer than 2 cm apart. Wheal size was recorded after 15 to 20 minutes.[28] SPT results were defined as positive with a mean wheal diameter of 2 mm or more than the negative control.

Blood was drawn from some patients for radioallergosorbent testing (RAST) for echinacea-reactive immunoglobulin (Ig)E, which was performed as previously described[29] by the Kolling Institute for Medical Research, Sydney. Results were compared with 3 negative control assayed in parallel. Radio-iodine uptake greater than 3 times the mean of negative control sera (NCS) was considered to represent a positive result. Results were reported by the clinical laboratory as follows: 1 + (3 to 5 × NCS value), 2 + (5.1 to 10 × NCS), 3 + (10.1 to 20 × NCS), or 4 + (>20 × NCS). An additional 24 stored sera were assayed by the same clinical laboratory, derived from samples sent for clinical testing in patients with asthma, allergic rhinitis, atopic dermatitis, drug allergy, anaphylaxis, and angioedema.

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) maintains a database of voluntary reports of suspected adverse drug reactions which is a public document. Anonymous reports involving CAM were obtained from ADRAC and reviewed. Reactions involving echinacea were examined in greater detail. Cases were considered to be possibly consistent with IgE-mediated hypersensitivity if one or more reactions (urticaria, angioedema, bronchospasm, anaphylaxis) was reported.

Additional data were obtained from the reporting doctors and pharmacists via anonymous surveys distributed by the TGA of the Australian Commonwealth Department of Health. Each reporter was questioned about demographic characteristics, intercurrent atopic disease, the time between ingestion and the reaction, whether the patient had taken it before, the use of other medication, their opinion as to causality, general comments about the reaction, and missing data from the report forms. Serum was collected from patients for further analysis where possible. Other international government drug agencies were also contacted for information regarding adverse reports involving echinacea.

A retrospective private office-based chart review was undertaken by RJM of 600 consecutively referred (predominantly atopic) patients seen in consultation in the years 1995 to 1997 (200 files per year) to determine the frequency of use of herbal products, including echinacea. A more detailed prospective survey of CAM use by 200 consecutively referred atopic patients was undertaken by one of the authors in March and April, 2000. Data were obtained from a routine preconsultation questionnaire completed by each patient, which included questions on use of prescribed medication, CAM, and echinacea. SPT of 100 of these subjects with glycerinated echinacea extract was also performed by RJM in his office practice.

RESULTS

Case Reports

Case 1. A 37-year-old female was referred for investigation of anaphylaxis after ingesting echinacea.[11] Within 5 minutes of ingestion of echinacea, she experienced burning throat, chest tightness, urticaria, and diarrhea, and required admission to hospital for treatment. She had ingested echinacea from the same bottle 2 weeks earlier uneventfully. She was known to be atopic and suffered from allergic rhinitis, oral allergy syndrome (OAS) with banana ingestion, and occasional wheeze. SPT was performed using commercially available glycerinated allergen extracts as previously described [11](Bayer Australia). SPT 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. Details of further investigation are shown in Table 1.

Case 2. A 19-year-old female suffered an acute asthma attack and severely itchy and watery eyes and runny nose within 10 minutes of her *first ever* exposure to echinacea-containing tea at 8 AM. Symptoms resolved gradually over several hours. She had intercurrent problems of seasonal allergic rhinitis, nasal polyposis, and sinusitis without asthma. No other food or medication had been ingested for >12 hours. SPT with the same brand of aqueous echinacea solution from case 1 (which had been shown to contain echinacea) a week later resulted in a 3-mm wheal (Table 1).

Case 3. Within 20 minutes of ingestion of an echinacea-containing tablet, a 31-year-old health professional suffered generalized urticaria, facial and upper airway angioedema, difficulty swallowing, bronchospasm, dizziness, and disorientation. Symptoms resolved

Table 1. Results of Investigation of Adverse Reactions Associated with Echinacea

Investigations	Case 1	Case 2	Case 3	Case 4	Case 5
Echinacea RAST (% iodine uptake)	4.4%	1.6%	1.4%	0.7%	Not available
Uptake/control uptake	14.7	5.3	4.7	2.4	–
Echinacea RAST score*	2+	1+	1+	Negative	–
SPT Echinacea	3 mm	2 mm	0 mm	2 mm	0 mm
SPT *Ambrosia sp*	2 mm	0 mm	2 mm	0 mm	0 mm
SPT *Lolium perenne*	10 mm	7 mm	8 mm	8 mm	0 mm
SPT *Phalaris canariensis*	8 mm	10 mm	7 mm	6 mm	–
SPT *Plantago sp*	8 mm	0 mm	1 mm	8 mm	0 mm
SPT *C. dactylon*	12 mm	6 mm	4 mm	2 mm	0 mm
SPT *D. pteronyssinus*	10 mm	1 mm	8 mm	0 mm	0 mm
SPT *D. farinae*	8 mm	3 mm	5 mm	0 mm	0 mm
SPT *F. domesticus*	5 mm	4 mm	9 mm	2 mm	0 mm
SPT *C. familiaris*	0 mm	0 mm	2 mm	0 mm	0 mm

* Skin prick test results are tabulated as weal size in mm. RAST results were scored by the reporting laboratory, with positive results defined as % radio-iodine uptake at least 2.5 above the mean of 3 negative control sera assayed in parallel. The ratio of test/control sera is also described.

gradually over several hours. During 3 of the preceding 4 days, she had taken the same echinacea tablets and had experienced headache and mild facial angioedema within 20 minutes of each administration but no reaction on the echinacea-free day. The patient was known to be allergic to latex and had a long history of perennial allergic rhinitis with seasonal exacerbation. She complained that sulfite-containing dried fruit would trigger urticaria, flushing, mild wheeze, and nasal obstruction. On one occasion she had experienced an episode of exercise-related anaphylaxis. Further investigation implicated previous ingestion of rye or mushroom (4 to 5 mm SPT to both) or nonsteroidal anti-inflammatory agents. No further episodes have occurred with avoidance of these substances. The patient, a trained observer, could not recall exposure to these agents or latex on the days in question and considered the relationship of reactivity to echinacea ingestion to be consistent and, in high probability, causative. SPT with the same aqueous echinacea solution from case 1, 1 year later, was negative (Table 1).

Case 4. A 56-year-old male reported the new onset of documented asthma coincident with the ingestion of echinacea tablets for treatment of an intercurrent upper respiratory tract infection. On three separate occasions, he developed severe difficulty breathing and coughing within 2 hours of ingestion of these tablets. He had intercurrent problems of allergic rhinitis. There was no known food or drug allergy, and he had taken no other medication during this period. Symptoms resolved within a few days of stopping echinacea. SPT with the same aqueous echinacea solution from case 1, 6 months later, was negative (Table 1).

Case 5. A 48-year-old female experienced a maculopapular rash over thighs and abdomen within 2 days of ingestion of echinacea tablets which had been taken to prevent infection. The rash resolved within 1 week with use of topical steroids. A week later, she recommenced echinacea from the same bottle and redeveloped a similar but more severe and generalized pruritic rash within 48 hours. It settled gradually over a period of 6 weeks and required a course of oral steroids to assist resolution. She had intercurrent problems of nonallergic (vasomotor) rhinitis and took no regular medication. SPT with the same aqueous echinacea solution from case 1, 5 months later, was negative (Table 1).

Use of CAM by Australian Atopic Patients

A retrospective chart review from patients seen by RJM in consultation 1995 to 97 demonstrated that CAM use (including vitamin) had risen from 7.5 to 25%, and that echinacea use had risen from zero to 3 to 5% over the same period.[11] When a more detailed prospective survey was undertaken in March and April of 2000, 44% of patients were currently using a regular vitamin/mineral supplement and 24% were using CAM (excluding vitamins/minerals) other than echinacea. Of these, 73% had heard of echinacea and had some idea of its purported properties, 38% had used echinacea some time in their lives, and 15% had used echinacea in the previous 3 months.

Australian Reports of Adverse Reactions to CAM

When interpreting Australian and international adverse drug reports, it is important to bear in mind that 1) the data represent voluntary reports of adverse events; 2) the reports may be incomplete; 3) the number of reports may not be indicative of the prevalence of adverse reactions; 4) association of a medication with an adverse outcome is not in itself proof that the medication in question caused the reaction; and 5) the reported event may have another explanation.

Between January 1979 and March 10, 2000, 483 reports involving CAM were reported to ADRAC. In two-thirds of cases, the CAM was the sole medication taken and was held responsible for the reaction. The majority of reports of hypersensitivity reactions were linked to ingestion of royal jelly or echinacea. Forty-one of the 51 re-

ports associated with echinacea implicated this substance as the sole suspected trigger. Twenty-six of these were considered by the authors to be consistent with IgE-mediated hypersensitivity, in that one or more reactions of urticaria, angioedema, exacerbation of asthma, or anaphylaxis was described (Table 2).

Australian Reports of Adverse Reactions to Echinacea

Fifty-one adverse reaction reports involving echinacea were submitted to ADRAC from 7 of the 8 Australian states and territories. Reports were scattered throughout the year without a discernible seasonal distribution. Of reports that were not suggestive of immediate hypersensitivity, non-urticarial rash (12 cases) and hepatitis (7 cases) were the most common complaints. Other symptoms included fatigue, arthralgia or myalgia (4 instances each), headache or increased blood pressure (2 instances each), and 1 case each of dizziness, atrial fibrillation, vasculitis, acute renal failure, nausea, or epistaxis.

Twenty-six cases were identified as suggestive of IgE-mediated reactions. Most were young female adults (median age 32 years, 80% female), of which the youngest (2 years old) suffered from facial and periorbital edema. Four patients required hospitalization for treatment of their allergic reaction. One subject (case 3 described previously) had three mild systemic reactions before anaphylaxis occurred.

At least six different brands involving at least three different formulations (tea, tablets, and liquid) were implicated. It was only possible to verify the presence of echinacea in one of these products with analysis using high-pressure liquid chromatography in the first[11] of the index cases (Dr. Patrick Purcell, TGA, personal communication).

Replies were received from 20 of 27 potential reporters, and 4 of these helped to exclude an allergic cause (1 case each of Henoch-Schönlein purpura, and subacute spongiotic dermati-

Table 2. Adverse Reactions Associated with CAM* in Australia

Medication	Death	Cardiac arrest	Anaphylaxis	Bronchospasm	Rhinitis	Urticaria	Angioedema	Allergic reaction	Sole suspected
Bee pollen			1						1
Walnut Oil				1					1
Celery Seed Extract				1					1
Cranberry						1			1
Echinacea†			4	12	1	14	6		13
Feverfew + Willow Bark						1			1
Garlic			1			1	1		0
Ginger						2	2		3
Ginseng§			1						0
Glucosamine HCl						1			0
Herbal laxative			1						1
Horseradish‡		1	1				1		0
Hypericum				2			1		1
Phytoestrogen compound						1	1		2
Propolis			1				3	1	5
Royal jelly	3	1	2	18	6	2	2		21
Valerian						1		1	2
Other unidentified medication	2	1		5		7	4	1	15
TOTAL	5	3	12	41	7	31	21	3	

* Data updated March 10, 2000.

† More than one symptom occurred in some cases.

‡ Echinacea also implicated.

§ Royal jelly also implicated in this reaction.

Between January 1979 and March 2000, 483 reports involving CAM were recorded in Australia, of which some were considered by the authors to be consistent with IgE-mediated reactions, defined as the presence of one or more of urticaria, angioedema, bronchospasm, or anaphylaxis.

tis with eosinophilia, photosensitive rash, and scalp itch).

More than 50% of the reports were from patients with known asthma, allergic rhinoconjunctivitis, or atopic dermatitis. Atopic disease was reported in 3 of 4 cases of anaphylaxis (1 unknown), 7 of 10 cases of bronchospasm (3 unknown), but only 1 of 12 cases of urticaria/angioedema (5 nonatopic, 6 unknown). Of the 4 subjects reacting within 1 hour of their first ever dose, 2 were known to be atopic and 2 were not (Fig 1). Three subjects reacted after their second ever dose (1 atopic, 2 unknown). No deaths were recorded. Symptoms appeared within 6 hours of ingestion in 62% of patients, within 12 hours in 75%, and within 24 hours in 94% of cases (information available for 16 of 26 subjects).

In the 24 of the 26 cases for which information was available, causality was indicated in the ADRAC data as certain (2 reports), probable (10 reports), or possible (12 reports). When asked their opinion as to the cause of the adverse reaction as part of this survey, all 17 respondents to the survey blamed echinacea. Echinacea was the sole medication being taken in at least 15 cases (4 unknown). The remaining 7 cases involved a total of 11 medications (Table 3).

Allergic Reactions to Echinacea: Allergy Testing of Australian Cases

Because there are few references to allergic reactions to echinacea in the literature, potential sensitivity to this plant was evaluated by adding in SPT for echinacea into the routine panel of allergens tested for in consecutive patients referred for evaluation of asthma or allergic rhinitis.[11] SPT of 100 atopic patients demonstrated reactivity to the same aqueous or glycerinated extracts of echinacea (defined as a wheal size at least 2 mm greater than the negative control) in 20% of patients; only three had ever ingested echinacea. Almost all subjects had strong reactivity to grass pollens on SPT (>90%). By contrast, SPT wheals to *Ambrosia sp.* were either negative or no greater than 2 mm.

RAST of 11 of 16 randomly selected stored sera from patients with allergic rhinitis, asthma, and atopic dermatitis demonstrated similar results (Table 4). Serum was available in only two additional "survey" cases for RAST. This resulted in 1.0% radio-iodine uptake in one case of anaphylaxis and 0.9% in one case of acute asthma with serum collected 2 years after the event. These were scored as borderline positive and negative, respectively, in that particular assay.

Reports to International Government Agencies of Adverse Reactions to Echinacea

A number of countries collect voluntary reports of adverse reactions to CAM. Information regarding reports associated with echinacea was provided by the Committee on Safety of Medicines (UK), the Special Nutritionals Adverse Event Monitoring System of the Food and Drug Administration (USA),[30] the Adverse Drug Reactions Monitoring Program (Canada), and the Center for Adverse Reactions Monitoring (New Zealand). Reports were considered by the authors to be consistent with IgE-mediated hypersensitivity if one or more reactions of urticaria, angioedema, exacerbation of asthma, or anaphylaxis was described These data are summarized in Table 5.

DISCUSSION

Fifty percent of Australians report using some form of CAM (apart from vitamins) in any 12-month period. Reasons given are to enhance well-being rather than to treat illness.[31,32] Nevertheless, these preparations are increasingly used to treat allergic disease as well.[7] Similar patterns of use have been noted in British and North American subjects.[33,34] Further, many Australian and British doctors either use CAM in their own practice or refer patients to practitioners who do.[35,36]

This popularity is reflected in the amount of money spent on CAM. In Australia, for example, this is more than the amount out of pocket spent on conventional medicine, estimated at >$900 million per year (approximately A$45 per person per year[31]). Expenditure in the United States is even higher, with an estimated doubling of expenditure from US$14 billion to $28 billion in the years 1990 to 1997 (approximately US$ 100 per person per year[33,37,38]).

Unfortunately, "natural" does not always equal safe. Some CAM interact with conventional medicines or are intrinsically toxic.[38,39] Because they are rarely packaged in childproof containers,[4] younger patients are at risk of accidental exposure. This is consistent with an estimated 400,000 reported cases of "poisoning" inquiries to American Poison Control Centers in 1996 associated with CAM.[3]

Hypersensitivity reactions have also been reported to CAM other than echinacea. Examples include royal jelly, pollen-containing preparations, chamomile, and other plant-derived com-

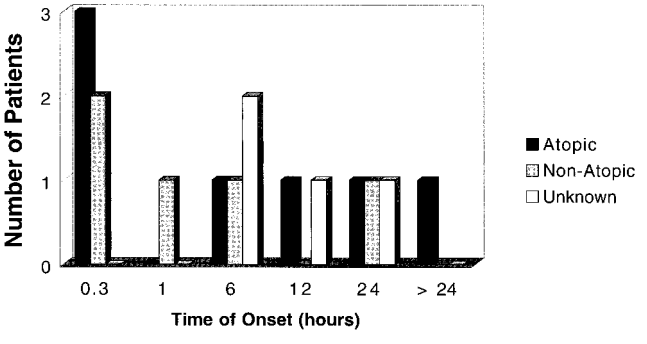

Figure 1. Onset of symptoms as a function of atopy. The onset of adverse reactions associated with echinacea is shown according to atopic status: atopic (*black bars*), nonatopic (*shaded bars*), and status unknown (*white bars*).

pounds.[8–10,41–44] This is not surprising when one takes into account the widespread use of CAM in the community and the propensity of atopic subjects to develop cross-reactive allergic responses to a variety of botanically or structurally related compounds.[45] Cross-reactivity may, in fact, be the explanation for the observation that four Australian subjects reacted to their first ever dose of echinacea, and one medically trained subject had several mild systemic reactions culminating in anaphylaxis (case 3). This is consistent with the presence of positive RAST and skin tests to echinacea in many of the personally observed cases, as well as 20% of asymptomatic atopic subjects, most of whom never ingested the plant.[11]

Table 3. Other Medications Used by Australian Patients with Possible Allergic Reactions to Echinacea

Case	Medication	Indication	Symptoms associated with echinacea
1	Inhaled beclomethasone, albuterol	Mild asthma	Severe asthma
2	Roxithromycin, dihydrocodeine, dexchlorpheniramine/ pseudoephedrine	Upper respiratory tract infection	Urticaria
3	Horse radish and garlic, allopurinol, enalapril	Hypertension, gout, upper respiratory tract infection	Angioedema
4	Ethinyloestradiol, levonorgestrel	Contraception	Anaphylaxis
5	Intranasal beclomethasone	Allergic rhinitis	Severe asthma
6	Topical betamethasone valerate	Atopic dermatitis	Urticaria
7	Vitamin preparations	Enhance well-being	Anaphylaxis

Of the 26 reports considered to be consistent with IgE-mediated hypersensitivity, Echinacea was the sole medication ingested in 15 cases, whereas 7 patients were taking other medication and no information was available in the remaining 4 cases.

There are many precedents for clinical cross-sensitization between ingested and inhaled allergens. For example, pollen-containing CAM have triggered anaphylaxis[42,43] and others (eg, royal jelly) contain pollen-derived allergens.[10,46] Patients who are allergic to ragweed and mugwort pollen, for example, may be clinically sensitive to watermelon, banana, honey, and royal jelly.[10,47,48] Sensitization via the respiratory route has even been postulated to explain some allergic reactions to food, including sunflower seeds and crustaceans.[49,50] OAS is common among grass, weed, and tree pollen-sensitive subjects, and anaphylaxis has been described under some circumstances.[51] Indeed, in a personal series of 430 patients evaluated for anaphylaxis, 78 of 262 of food-related episodes were triggered by the combination of exercise and ingestion of semi- or uncooked fruit and vegetables in patients with OAS (RJM, unpublished observations, 2000).

Despite its recent appearance in nurseries as an ornamental plant, exposure to echinacea pollen (and to Asteraceae [Compositae] weed pollen such as ragweed) is extremely limited in Australia. The implication is that for sensitization to occur, it must do so indirectly by exposure to more common members of that family, such as chrysanthemums, dahlias, sunflowers, marigolds, and daisies, or via cross-reactive foods such as those described above. Flowering Asteraceae (Compositae) are not only popular ornamental plants, but exposure to plants growing in the wild is common in arid areas of Australia, where it is a common cause of "Australian bush dermatitis."[52] However, allergens have been identified that are common to Asteraceae (Compositae) and pollinating grasses.[53] It is uncertain, however, whether the high frequency of grass sensitivity in patients with positive skin tests to echinacea[11] supports cross-reactivity is simply a marker of atopy, or reflects contamination of echinacea products with grass pollen-derived allergen.

The Australian data provide the best evidence to date of an uncommon potential for serious allergic reactions to echinacea in atopic patients, similar to that reported previously in association with allergic reactions to royal jelly.[8–10] Echinacea accounts for >10% of adverse reports involving CAM in Australia, with >50% exhibiting consistent-seeming IgE-mediated hypersensitivity. Atopic patients seem to be at particular risk. More than two-thirds of patients who suffered from acute asthma attacks or anaphylaxis were atopic. The reliability of the data is enhanced by having had direct contact with the majority of the reporters for additional information and the direct evaluation of five of these by consultant physicians in clinical immunology and allergy.

Similar reports of adverse reactions to echinacea have been recorded in several international databases. Although caution must be used when interpreting voluntary reports of adverse drug reactions, a relationship between a medication and an adverse reaction is more likely when: 1) only one medication is implicated; 2) the reactions can not be easily explained by an underlying medical condition; 3) the onset of symptoms occurs soon after ingestion of the drug; 4) the reaction is consistent with a known property of the preparation; 5) one can identify a particular population at risk by means of age, sex, or underlying disease; and 6) there is a mechanism for confirming the relationship by specific testing or rechallenge. None of the patients seen by the authors in consultation were

Table 4. Echinacea RAST in Atopic Control Subjects

History	Echinacea RAST (% iodine uptake)	RAST grade	Echinacea RAST (test/control ratio)	Other positive RAST
Asthma	10.6	3+	17.7	House dust mite
Asthma, anaphylaxis to royal jelly (fatal)	9.4	3+	15.7	House dust mite, cat, royal jelly
Asthma	4.7	1+	7.8	House dust mite
Asthma	4.2	1+	7.0	House dust mite
Allergic rhinitis	2.5	1+	4.2	House dust mite, cat, cockroach
Allergic rhinitis	3.4	1+	5.7	House dust mite, cat, grass
Allergic rhinitis	5.3	2+	8.8	House dust mite, cat, grass
Allergic rhinitis	3.6	1+	6.0	House dust mite, mold, grass
Allergic rhinitis	1.3	–	2.2	House dust mite, weeds, grass
Allergic rhinitis	1.6	–	2.7	House dust mite, grass
Allergic rhinitis	1.0	–	0.2	House dust mite
Allergic rhinitis	1.7	–	2.8	Ryegrass
Allergic rhinitis	0.5	–	0.8	Grass
Atopic dermatitis	23.9	4+	39.8	House dust mite
Atopic dermatitis	4.1	2+	6.8	House dust mite, cat, grass, weeds, mold
Atopic dermatitis	2.2	1+	3.7	House dust mite
Drug reaction	19.6	4+	32.7	Cephalosporins
Drug reaction	19.2	4+	32.0	Cephalosporins
Drug reaction	12.4	4+	20.7	Cephalosporins
Drug reaction	1.6	–	2.7	Scopolamine
Anaphylaxis	24.0	4+	40.0	Nuts
Anaphylaxis	2.6	1+	4.3	Nuts
Anaphylaxis	1.6	–	2.7	Chinese herbal remedy
Angioedema	1.2	–	2.0	Grass, mold
Normal sera	0.6	–	1.0	–
Cord serum	0.3	–	0.5	–

Stored sera were assayed for echinacea-binding IgE. RAST results were scored by the reporting laboratory, with positive results defined as % radio-iodine uptake at least 2.5 standard deviations greater than the mean of 3 negative control sera assayed in parallel. The ratio of test/control sera is also described. Additional clinical information is listed, where known.

willing to undergo deliberate challenge with echinacea.

At least six different brands involving at least three different formulations (tea, tablets, and liquid) were implicated in Australian reports. This suggests that echinacea itself (rather than a contaminant or excipient) was responsible for the reaction. Echinacea was the sole implicated trigger in at least 15 of 26 patients. In the remaining 7 patients taking other medications, the reaction reported might be explained by either medication or underlying disease process in only the first 3 cases (Table 3). For example, angioedema is a potential complication of use of angiotensin-converting enzyme inhibitors,[54] and acute bronchospasm or urticaria could have been triggered by infection for which echinacea was taken.[55,56]

Although non-IgE–mediated mechanisms have been proposed to explain some "allergic syndromes" related to medication,[57,58] more than two-thirds of patients suffering from serious symptoms of asthma or anaphylaxis were atopic. A role for allergy is supported by evidence of positive SPT results or RAST to echinacea in 4 of the 5 patients seen personally (2 of 4 positive to both; 2 of 4 positive to RAST *or* skin tests) and the onset of symptoms within 1 hour in at least 6 of the 16 patients for whom information was available. Although these patients declined specific rechallenge, at least three reported repeated"challenges" and symptoms after ingestion of echinacea.

The increasing popularity of echinacea is consistent with the high level of community awareness and use of echinacea by atopic patients in this study; the estimated 200 million doses consumed in Australia per year (equivalent to 10 doses per person per year)[14] and the 68% increase in echinacea's herbal medicine market

Table 5. International Reports of Adverse Reactions Associated with Echinacea

	Food and Drug Administration (U.S.A.)	Committee on Safety of Medicines Yellow card Scheme (U.K.)	Adverse Drug Reactions Monitoring Programme (Canada)	Centre for Adverse Reactions Monitoring (New Zealand)
Total reports	52	9	12	2
Number of cases consistent with IgE-mediated hypersensitivity*	6	3	2†	1
Date of update	Oct 20, 1998	March 28, 2000	April 3, 2000	April 8, 2000
Anaphylaxis			1	
Exacerbation of asthma		1		
Non-urticarial rash	2		1	
Urticaria	2	2	1	1
Angioedema	2		1	

* Reports were classified by the authors.

† More than one symptom described.

Adverse drug reports involving echinacea were obtained from several international drug agencies and classified by the authors as being consistent with IgE-mediated hypersensitivity if one or more of urticaria, angioedema, exacerbation of bronchospasm, or anaphylaxis were described.

share in the United States between 1995 and 1996.[38]

The safety of any product is a relative concept which takes into account the potential for toxicity in the entire population as a whole, as well as those at particular risk by virtue of age, sex, organ dysfunction, or atopy. As has been observed with royal jelly,[8,10] atopic patients seem to be at particular risk of developing potentially life-threatening allergic reactions to echinacea. It is conceivable that relatively minor reactions such as transient rashes or aggravation of underlying asthma may go unnoticed and unreported.

CONCLUSION

It is naïve to assume that natural products are always safe. Indeed, given the popularity of echinacea, even rare adverse events become inevitable when a large proportion of the population uses it mostly unsupervised. Because these reactions may occur with even their first ever known exposure, atopic patients should be cautioned appropriately.

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