CONFERENCE PAPER

Drug Safety 2008; 31 (5): 419-423
0114-5916/08/0005-0419/$48.00/0

Surveillance of Suspected Adverse Reactions to Natural Health Products

The Case of Propolis

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Abstract

Natural health products are promoted to the public as equally or more effective and less toxic than conventional drugs. However, some 'natural' medicines are known to have adverse effects.

From April 2002 to August 2007, 18 suspected adverse reactions associated with propolis-containing products were reported to the national surveillance system of natural health products, coordinated by the Italian National Health Institute. Sixteen reports concerned allergic reactions (with dermatological or respiratory symptoms), while two concerned the digestive tract. Some of the reactions were serious: six patients were admitted to hospital or visited an emergency department and in two of these a life-threatening event was reported. In seven patients (four of whom were children), an allergic predisposition was indicated.

Propolis, a resinous substance collected by honeybees from the buds of living plants, has been used for several purposes (dermatitis, laryngitis, oral ulcers) because of its wide range of suggested activities (antibacterial, antiviral, anti-fungal, anti-inflammatory, antioxidant and chemopreventive actions). However, propolis is also a potent sensitizer and should not be used in patients with an allergic predisposition, in particular an allergy to pollen.

In Italy, products containing bee derivatives (bee pollen, royal jelly or propolis) are available to the public as food supplements. No label warning of possible adverse reactions is found on the packaging, although it is well known that atopic and asthmatic individuals may be at an increased risk of allergic reactions after using these products. The public and healthcare practitioners should be aware of the risk of allergic reactions to products derived from bees and a warning should be added to the packaging of these products.

Propolis is the generic name of a natural dark-coloured resinous substance collected by honeybees from the buds of living plants, such as *Cistus* spp., *Clusia* spp. and *Populus* spp. Propolis is a mix of bee wax and salivary secretions. It has been used for several purposes (dermatitis, laryngitis, oral ul-

cers)[1] because of its wide range of suggested activities, which include antiviral, antifungal, antibacterial (Gram-positive and -negative bacteria), anti-inflammatory, antioxidant and chemopreventive actions.[2,3] The chemical composition of propolis varies depending on its geographic region, and it is very complex as >300 compounds have been identified. The general composition is 50% of resin and vegetable balsam, 30% of wax, 10% of essential oils, 5% of pollen and 5% of organic debris.[3] In Europe, the presence of polyphenols, coumarins, amino acids, steroids and inorganic compounds has been reported. The biological activities are mainly attributed to flavonoids (rutin, quercetin, galangin) and to phenolic acids with their esters (caffeic acid phenethyl ester as a major component).[2,4] Propolis seems relatively safe, with a calculated safe dose of 1.4 mg/kg bodyweight/day in humans (applying the safety factor of 1000).[5] Nevertheless, propolis is a potent sensitizer and is a well recognized cause of occupational allergic eczematous contact dermatitis in apiarists.[6] For this reason, propolis is contraindicated in patients with an allergic predisposition, in particular an allergy to pollen. The allergenic action seems to be due to caffeic acids derivates.[7] In this paper, we present the suspected adverse reactions associated with propolis reported within the surveillance system of natural health products active in Italy since 2002.

1. Surveillance System

The Italian Pharmacovigilance System collects spontaneous reports of adverse reactions only for registered drugs; however, awareness of the need for surveillance of the safety of natural health products has stimulated the implementation of a suspected adverse reactions reporting system in Italy, set up by the Italian National Institute of Health (Istituto Superiore di Sanità).

An *ad hoc* reporting form, similar to that in use to collect spontaneous reports of suspected adverse reactions to conventional drugs, was defined. The form was adapted to reporting suspected adverse reactions to any kind of natural health product (raw medicinal plants, dietary supplements, animal-derived products, minerals, homeopathic preparations, etc.), which are not included in the pharmacovigilance system.

Voluntary reports of suspected adverse reactions are sent by the reporters (hospital doctors, office-based specialists, general practitioners, pharmacists) to the National Institute of Health, where all the forms are collected and registered in a centralized database. All reports are individually evaluated by a multidisciplinary group of experts (in the fields of epidemiology, pharmacology, pharmacognosy, toxicology, phytotherapy, homeopathy, pharmacovigilance).

The serious clinical events (deaths, life-threatening events, requiring or prolonging hospitalization or significantly disabling) are analysed more in depth by the group and written reports are sent to the Italian Medicines Agency for possible regulatory actions.

2. Suspected Adverse Reactions

Eighteen suspected adverse reactions associated with propolis-containing products were reported from April 2002 to August 2007 (table I). Six cases involved children (aged 1–10 years). One patient was a pregnant woman who used the product for acute pharyngitis in the first weeks of pregnancy (15 weeks). Sixteen reports concerned allergic reactions (with dermatological or respiratory symptoms), while two concerned the digestive tract. Some of the reactions were serious: six patients were admitted to hospital or visited an emergency department and in two of these patients a life-threatening event was reported. In seven patients (four of whom were children), an allergic predisposition was indicated. A positive rechallenge was observed in a 63-year-old woman, who had experienced a similar reaction using a mouthwash some years earlier.

Propolis was used in almost all cases for upper respiratory tract infections, or as topical preparations (cream and mouthwash) for wound healing (in a 1-year-old child) or for mouth ulcers.

Table I. Clinical data of adverse reactions associated with the use of propolis products

Age (y), gender	Trade name[a]	Product components other than Propolis	Daily dose (route of administration); duration	Reason for use	Adverse reactions	Positive dechallenge; positive rechallenge	Hospitalization or ED visit/applied therapy	Other medications/ conditions
1, M	Galenic (10% Propolis)	NR	When needed (topical); 14 d	Healing wounds and itching relief for atopic dermatitis	Atopic and generalized eczema, with impetigo	Yes; NR	Yes/antibacterials (PO) + corticosteroids and antibiotics (topical)	*Cedrus libani*, Sulphur 30 CH, and dropropizina/NR
4, M	Apropos A®, Propoli EPID C®	Ginkgo, *Helichrysum* sp., *Ribes nigrum*, mint, tea tree oil, thyme, grapefruit, *Rosa canina*	2 vials/d (aerosol) + 2 tablets/d (PO); 4 d	Influenza	Acute asthma	Yes; no	No/corticosteroids	No/atopic patient
5, F	Apropos A®, Propoli EPID C®	Ginkgo, *Helichrysum* sp., *Ribes nigrum*, mint, tea tree oil, thyme, grapefruit, *Rosa canina*	2 vials/d (aerosol) + 2 tablets/d (PO); 5 d	Influenza	Acute asthma	Yes; no	No/corticosteroids	No/atopic patient
5, F	Propolis spray		NR	Pharyngitis	Scattered anthema with itch and modest lower and bilateral blefaroedema	Yes; no	Yes/NR	None/none
10 M	Gol-Natur Lenigola®	Water, fructose, concentrated apple juice, povidone, glycine, sorbitol, silica, aroma, cellulose, potassium sorbate, methyl p-hydroxybenzoate, acesulfame-K	2 oral sprays, twice/d; 2 d	Tonsil inflammation	Cutaneous rush	No; no	No/antihistaminics	No/familial atopia
10, M	Propolis		NR (oral spray); 2 d	Tonsils hypertrophy	Cutaneous rush	No; no	No/antihistaminics	NR/familial allergic asthma
30, M	Propolis		2 tablets/d (PO); 2 d	Sore throat	Allergic reaction (erythema)	Yes; no	Yes/corticosteroids	Barbiturates/infant epilepsy

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Table I. Contd

Age (y), gender	Trade name[a]	Product components other than Propolis	Daily dose (route of administration); duration	Reason for use	Adverse reactions	Positive dechallenge; positive rechallenge	Hospitalization or ED visit/applied therapy	Other medications/ conditions
34, F	Propolis		Once/d (topical use); 2 d	Acute pharyngitis	Labial oedema, with tongue paraesthesia	No; NR	Yes/corticosteroids	NR/pregnant woman (15 wk)
35, M	Propolis pomade		NR (topical use), NR	NR	Toxic local dermatitis (chest and hands)	NR; NR	No/NR	NR/NR
36, F	Propolis		1 topical; 1 d	Pharyngodynia	Asthma episode	Yes; no	Yes/corticosteroids + β_2-agonists	Propylthiouracil/allergy
37, F	Propolis mother tincture		12–20 drops, 2–3 times/d (PO), for 4 mo	Sore throat	Gastroesophageal reflux with heartburn	Yes; no	No/protonic pump inhibitors	Occasionally, sodium ferrogluconate/allergic rhinitis
40, F	Lenigola Spray Forte®	Alcohol (ethanol), water, glycerin, thyme and eucalyptus e.o.	1 oral spray, 3 times/d (PO); 1 d	Tonsils inflammation	Breath impairment	Yes; no	No/none	NR/none
43, M	Propolis mouthwash		NR, 1 d	Mouth aphtha	Oedema of uvula and tongue	NR; NR	NR/corticosteroids + antihistaminics	NR/NR
51, F	PropolPur spray®	Glycerin, water, *Citrus limonum* e.o.	3 oral spay/d; 2 d	Pharyngitis	Face oedema	NR; NR	No/NR	None/none
57, M	Propolis		20 drops/d (PO); 3 d	Sore throat	Labial and tongue oedema	Yes; NR	No/corticosteroids + antihistaminics	NR/NR
61, F	Propolis		20 drops, twice/d (PO); 2 d	Common cold	Digestive difficulties with stomach ache	Yes; NR	No/yes, but the therapy was NR	None/none
63, F	Lenigola Propoltimo®	Acerola, thyme e.o., sucrose, lactose, orange flavour	1 tablet/d; 1 d	Pharyngitis	Uvula and soft palate oedema	Yes; yes	Yes/corticosteroids + antihistaminics	Flurbiprofen mouthwash/ previous allergic reaction to mouthwash, containing Propolis
91, F	Grindoral tablets®	Brown sugar, milk powder, *Grindelia* sp., eucalyptus e.o., mint e.o.	NR	NR	Labial, tongue and palate oedema	Yes; NR	No/NR	Atorvastatin, pentoxyfilline and indobufen/NR

a Where not differently specified trade name was NR.

ED = emergency department; **e.o.** = essential oil; **F** = female; **M** = male; **NR** = not reported; **PO** = oral administration.

3. Conclusion

In Italy, products containing bee derivatives (bee pollen, royal jelly or propolis) are available to the public as food supplements, without any label warning of possible adverse reaction, although it is well known that atopic and asthmatic individuals may be at an increased risk of allergic reactions after using these products.[8-10] Propolis-containing products are often a mixture of various components that could contribute to adverse events. In particular, when essential oils are involved, high doses of the potential active ingredients are present. Furthermore, spray formulations were often used from our cases and this way of administration is particularly dangerous when allergenic substances are inhaled.

The public and healthcare practitioners should be aware of the risk of allergic reactions to products derived from bees and a warning should be added on the packaging of these products.

Acknowledgements

No sources of funding were used to assist in the preparation of this conference paper. The authors have no conflicts of interest that are directly relevant to the content of this conference paper.

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