SHORT COMMUNICATION

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Allergic Reactions to Medicines Derived from *Pelargonium* Species

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Abstract

Pelargonium (*Pelargonium sidoides* DC and *P. reniforme* Curtis) is reported to have immune modulating properties and antibacterial activity, and *Pelargonium* extracts have been used for the treatment of respiratory tract and gastrointestinal infections. Introduced in the early 1980s in Germany, Umckaloabo® (ISO Arzneimittel), an ethanolic extract of the roots of *P. sidoides* and *P. reniforme*, was the first *Pelargonium*-derived product to be commonly used in a country in the EU. According to the Umckaloabo® product information, this extract has no known adverse effects. However, there is a theoretical risk of interactions with anticoagulants such as warfarin, and antiplatelet drugs, such as aspirin (acetylsalicylic acid). To date, the Uppsala Monitoring Centre has, through the WHO international pharmacovigilance programme, received 34 case reports of allergic reactions suspected to be associated with the use of *Pelargonium* extract, all originating from Germany. In a number of these reports, the description and timing of the event was indicative of an acute Coombs and Gell Type I hypersensitivity reaction; two of these patients needed treatment for circulatory failure. So far, the experience of such reactions is limited to Germany. Since *Pelargonium*-containing herbal products have recently been approved in a number of other countries, the possibility of the occurrence of allergic reactions has become of more general interest and further information regarding these products is needed.

The botanical ingredients *Pelargonium reniforme* and *P. sidoides* are closely related species that occur commonly in the Eastern Cape Province of South Africa, and can be distinguished from each other by a combination of petal colour, petal shape and sepal colour.[1] Extracts of the roots of these species are reported to have immune modulating properties and antibacterial activity and have been used for the treatment of respiratory tract and gastrointestinal infections. The use of *Pelargonium* spp. as a medicine is based on that of traditional Zulu healers and has been known to modern science since the 1890s.[2]

Introduced in 1983 in Germany, Umckaloabo®[1] (ISO Arzneimittel) is the first commonly used product derived from *P. reniforme* and *P. sidoides* to be marketed a country in the EU. In 2002, Umckaloabo® had an annual sale value of €55 million (4.1 million packages sold).[3] Umckaloabo® is sold as an ethanolic tincture with a recommended dosage

1 The use of trade names is for product identification purposes only and does not imply endorsement.

of 20 drops orally, 3–5 times per day.[4] The name Umckaloabo is derived from two Zulu words: *umkhuhlane* (fever and cough-related diseases) and *uhlabo* (pleurisy-related chest pain), representing the indications for use. According to the Umckaloabo® product information, there are no known adverse effects.[4] However, there is a theoretical risk of interactions with anticoagulants such as warfarin, and antiplatelet drugs such as aspirin (acetylsalicylic acid). There are also cautions against use by patients with serious liver or kidney diseases or during pregnancy.[4] Recent randomised, double-blind, placebo-controlled studies of the treatment of acute bronchitis with an extract of *P. sidoides* (EPs 7630) assessed the adverse reactions observed as being nonserious[5] or minor and transitory.[6]

In the US and Canada, ethanolic extracts of *P. sidoides* have been marketed as a dietary supplement by Nature's Way under the name Umcka™ since 2003. Although not available in the UK at present, Nature's Way was granted a trademark for Umcka™ in 2005. Umcka™ is available in different strengths, all of which are administered orally.

The Uppsala Monitoring Centre (UMC) maintains the WHO international pharmacovigilance programme, in collaboration with national pharmacovigilance centres in 80 countries around the world.[7] The UMC receives case reports of suspected adverse drug reactions, which are stored in a structured International Conference on Harmonisation (ICH) E2B-compatible, 3rd revision, summary format in a central database (Vigibase). The case reports are anonymous and heterogeneous and vary with regards to their source, documentation and likely relationship to the drug administered.

In the period from 2002 to 2006, the UMC received 34 case reports of hypersensitivity reactions that were suspected to have been induced by Umckaloabo®, all originating from Germany (table I). All reports but one were from pharmacists, in reaction to complaints by patients, to the regulatory authority in Germany.[8] All original reports were requested and reviewed individually. In ten reports, concomitant use of other drugs was noted, but none of the concomitantly administered medications were recorded as being co-suspect. In 15 of the 34 reports, the description and timing of the event, notably the combination of a skin rash with itching, urticaria, angioedema and/or systemic involvement (e.g. dyspnoea/bronchospasm, diarrhoea, tachycardia or circulatory failure), were suggestive of a Coombs and Gell Type I acute hypersensitivity reaction; three patients had conjunctivitis and two rhinitis. Two of the patients needed treatment for circulatory failure or anaphylactic shock; however, insufficient information was provided to determine if they had experienced anaphylactic shock. Further details of these two reports are provided below:

Case report 1, concerning a 20-year-old woman, was reported by a dermatologist. After taking Umckaloabo® drops for a common cold the patient experienced life-threatening acute urticaria and circulatory failure, necessitating hospital admission. The reaction subsided within 4 hours of initiation of corticosteroid and antihistamine treatment. The patient had not received any other drugs and a positive skin-prick test confirmed the causal involvement of Umckaloabo®.

Case report 2 was submitted by a pharmacist to the Medicines Committee of the German Pharmaceutical Association. The patient was a 71-year-old man who, within a day after first taking Umckaloabo® drops, experienced an allergic reaction in association with dyspnoea and swelling of the lips and tongue, requiring medical treatment.

Based on the reports of suspected adverse reactions, the regulatory authority in Germany[8] has recently decided that the following information will be added to the product information of Umckaloabo®: "After intake of Umckaloabo®, gastrointestinal complaints (gastric pain, heartburn, nausea, diarrhoea) commonly occur. In many cases, it cannot be differentiated whether the symptoms are caused by the preparation or by the underlying disease. Gingival bleeding or epistaxis may occur rarely. In rare cases, hypersensitivity reactions were reported (exanthema, urticaria, mucocutaneous pruritus) after first or repeated intake. Very rarely severe hypersensitivity reactions with facial oedema, dyspnoea and hypotension may occur."

Herbal drugs usually contain substances with antigenic properties (e.g. terpenes, coumarins, proteins or glycosides). While sensitisation is more common after infection and topical application, it is of interest that with Umckaloabo® hypersensitivity reactions occurred already after oral administration.

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Table I. Case reports of allergic reactions suspected to be connected with the use of Umckaloabo® [a]

Case report	Sex	Age	Suspected adverse reactions (WHO-ART terms)	Concomitant	Days of use
1	F	43	Rash, pruritus	None	1
2	F	50	Rash erythematous, face oedema, oedema peripheral, allergy	None	1
3	M	10	Pruritus	None	3
4	M	68	Allergic reaction, dermatitis, flushing, dry skin, oedema, conjunctivitis	Selenium, calcium, vitamin A	1
5	F	32	Rash	NL	10
6	F	50	Acne, pruritus, headache, oedema mouth	None	2
7	F	39	Rash	None	2
8	M	12	Rash, pruritus	None	3
9	M	35	Feeling of warmth, dizziness, tachycardia	None	3
10	F	60	Rash, pruritus	None	3
11	F	40	Dyspnoea, allergic reaction	None	NL
12	M	7	Pruritus, pharyngitis, coughing, asthma	None	1
13	F	60	Asphyxia, allergic reaction	None	NL
14	F	45	Rash papular	None	2
15	M	59	Rash, pruritus, oedema	None	2
16	F	18	Flushing, pallor, dizziness, vision abnormal	None	NL
17	F	NL	Rash erythematous, paraesthesia, dyspnoea, allergic reaction	None	NL
18	F	NL	Dermatitis, allergic reaction	None	NL
19	M	5	Rash erythematous, allergic reaction, bullous eruption, pruritus	Ambroxol	5
20	M	46	Rash erythematous, rash pustular, pruritus, dysphagia, face oedema, allergic reaction	Aspirin (acetylsalicylic acid) plus vitamin C	1
21	F	40	Dermatitis, pruritus	None	1
22	F	63	Conjunctivitis, asthma, allergic reaction	Dexpanthenol/xylometazoline	NL
23	F	63	Rhinitis, epistaxis, bronchial obstruction, therapeutic response decreased	None	NL
24	F	20	Urticaria acute, circulatory failure	None	NL
25	F	70	Rash pustular, cheilitis	None	12
26	M	57	Rash, flushing, allergy	None	8
27	M	71	Tongue oedema, dyspnoea, anaphylactic shock, oedema mouth	None	2
28	F	63	Rash, pruritus, sweating increased	Bisoprolol	1
29	F	70	Rhinitis	Budesonide	NL
30	M	38	Dermatitis, rash, rash erythematous, pruritus	None	3
31	M	14	Allergy, urticaria (generalised, pruritus)	None	2
32	F	75	Allergy, conjunctivitis, rhinitis	Cevitect® thymian lozenges	NL
33	F	34	Allergy (skin and mucosa)	Spasmo mucosolvan®, levothyroxine sodium	1
34	F	27	Rash, pruritus, tachycardia, diarrhoea, epitasis	Gelo-bronchial®	3

a The table presents the data as available in the original reports. In many cases, the information was limited. Persistent injury was not recorded in any of the reports. There were no rechallenge experiences. Genetic predisposition information is unavailable.

F = female; **M** = male; **NL** = not legible; **WHO-ART** = WHO adverse reaction terminology.

It is of note that allergy – i.e. contact dermatitis, contact urticaria and toxicoderma – to *Pelargonium* house plants as a result of contact with aerial parts has previously been documented.[9-11] Once exposure to the allergen is stopped, acute hypersensitivity reactions are usually of limited duration. There-

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fore, 'dechallenge' information is, in this case, of little interest. In patients with suspected hypersensitivity, re-exposure to the drug is dangerous and a 'rechallenge' is contraindicated. In this light, the absence of reports with rechallenge information is not a surprise. So far, pharmacovigilance information is limited to the experience with Umckaloabo® in Germany. Since *Pelargonium*-containing herbal products have only recently been, or will be, marketed in a variety of other countries, the possibility of the occurrence of allergic reactions has become of general interest; further information regarding these products in needed. Future reports of suspected adverse reactions to *Pelargonium*-containing herbal products can be very significant for the early detection of adverse reactions.

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