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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

FINAL

PUBLIC STATEMENT ON THE ALLERGENIC POTENCY OF HERBAL MEDICINAL PRODUCTS CONTAINING SOYA OR PEANUT PROTEIN

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Remark: The final version of the guideline "Excipients in the label and package leaflet of medicinal products for human use" has been published in July 2003. Information on cross-reactions of peanut and soya has been included in the texts for peanut oil and soya oil, a general threshold of zero is stipulated. No warnings for soya lecithin are listed. This specification of excipients contrasts to the recommendations for active compounds given in this paper.

Since no assessment report is available, and no further information was given on request, the decision-making process for the guideline cannot be commented.

Besides that, no new data have been published since June 2003, which afford a revision of the statements outlined below.

Clinical problem

Soya protein and peanut protein are known to cause severe and potentially live-threatening type I allergic reactions. The relevance of these allergens is highlighted by a Swedish investigation, which revealed that 45 out of 61 severe allergic reactions to food were caused by soya, peanut or nuts. In 4 out of 6 fatal outcomes soya was the responsible allergen, in the 2 other cases peanut. In none of the 4 children who died due to a soya-induced anaphylaxis the allergy was known before, but all of them suffered from peanut allergy (Foucard et al., 1999). The suspected cross-reactions are confirmed by in-vitro experiments (Gall et al., 1990). IgE-cross reactions and severe clinical reactions to soya products are also reported for patients with birch pollen allergy and associated food allergies (Kleine-Tebbe et al., 2001). According to Vadas et al., 2001, more than 70 % of children with peanut allergy show reactions already at the first known time of ingestion. One possible way of sensitization is via breast-feeding since peanut protein was shown by the same authors to turn up in breast milk in amounts that may be sufficient to establish allergy. Furthermore, Lack et al. (2003) found a significant association between consumption of soya milk or soya formula in the first two years of life and the development of peanut allergy. About 90 % of individuals with peanut allergy were exposed to skin creams that contained peanut oil especially during the first six months of life.

Type I reactions to peanut/soya containing medicinal products

Several severe reactions to soya oil and/or soya lecithin after parenteral application of high amounts of soya oil (infusion of lipid emulsions or injection of drug preparations) have been reported (e.g. Andersen und Nissen, 1993, Weidmann et al., 1997, several serious adverse event reports). Reports on anaphylactic reactions after oral ingestion or topical administration of soya or peanut containing products were not found while severe anaphylaxis was described in several cases after consumption of dietary products containing soya protein or soya oil. After use of soya oil or peanut oil containing bath additives skin reactions were reported (possibly eczematic reaction to type I allergens in atopic patients).

Clinical trials

Skin tests and/or oral provocations with refined soya oil peanut oil did not point to substantial risks for allergic persons:

- 6 Patients with systemic allergic reactions to soya protein did not show symptoms after oral provocation with soya oil (Bush et al., 1985).
- 60 patients with peanut allergy were exposed orally to peanut oil in a double-blind controlled trial. While 6 patients showed symptoms after intake of crude oil no reaction to refined oil was seen (Hourihane et al., 1997).
- In 41 children with a positive in vivo or in vitro test against peanut, skin prick tests with refined and unrefined peanut oil were performed. While 15 children showed reactions to the unrefined oil none reacted to refined oil Kull et al., 1999).
- 10 patients who had experienced systemic reactions after peanut ingestions did not react in skin prick test or after oral provocation to peanut oil (Taylor et al., 1981).

Reports on clinical studies investigating the allergenicity of soya lecithin are not available.

Protein content in soya and peanut products

The protein content of peanut or soya products is process-related. According to Crevel et al. (2000) the protein content in crude plant oils (peanut, sunflower, coconut) is 100-300 mg/L while in refined proteins it is 0.2-60 mg/L. Deodorized oils (deodorization = heating to 230-250°C for 45-50 min) contain maximally 8 mg/L protein. It may be concluded that for completely refined oils a reduction of protein content by the factor 100 is achieved. Comparable studies on soya oils are not published, but a similar protein reduction may be assumed. Whereas validated methods for the protein determination in peanut oil exist, there is no validated methodology available for soy oil. However it has not been clarified if this reduction in all cases is sufficient for prevention of severe allergic reactions.

The protein content of soya lecithin seems to vary even more (0.006 – 2.7 %) according to the results of 2 studies with commercially available products (Müller et al., 1998, Porras et al., 1985). For medicinal purposes highly refined phosphatidylcholine with < 20 ppb protein is available.

Allergenicity of residual protein in soya and peanut products

Results on residual allergenic activity in refined oils are contradictory:

While some authors did not find IgE-binding in refined soya oils (Awazuhara et al., 1998, Paschke et al., 2001), Zitouni et al. (2001) found IgE-binding for crude soya oil with 1.89 mg/L protein as well as for refined oil with 0.32 mg/L protein. Porras et al. (1985) found soya protein in 3/20 samples but did not give further information on the purity of the tested soya oils. Allergenic activity was shown for peanut oil with 0.1-0.2 µg/g protein, as well (Olszewski et al., 1998). The differences may probably be explained by different degrees of refinement. The conclusion must be drawn that the term 'refined' peanut or soya oil cannot be translated into 'non-allergenicity'.

Results for soya lecithin are also contradictory. Paschke et al. (2001) found IgE binding in all tested soya lecithins (protein content 2,300 – 2,700 mg/kg). Awazuhara et al. (1998) demonstrated for soya oil proteins a markedly reduced IgE binding rate in soya allergic persons and no binding at all for soya oil protein. They concluded that soya lecithin has only a minor allergenic effect. Mueller et al. (1998) found residual IgE-binding in so-called standard lecithins. In deoiled lecithins only minimal or no reactions at all were detectable.

Loss of allergenicity due to thermic denaturation is not proven. According to Burks et al. (1992) heating does not reduce IgE- and IgG-bindings of peanut or soya oil protein.

Clinical relevance

In vitro IgE binding must not imply clinical risks in general since a minimal allergen dose is necessary for induction of a type I reaction. Investigations on threshold doses in established food allergy are limited but show that inter-individually varying minimal doses are necessary to trigger a reaction. 5 % of patients with peanut allergy reacted to an oral dose of 1 mg, 36 % showed symptoms after a cumulative dose of less than 100 mg. Below 1 mg only mild, questionable reactions were reported (oral itching), below 100 µg no reactions at all. For fish and ovalbumin allergy reactions were demonstrated at low doses of 5-10 mg. Routine allergen provocations are started mostly with ingestion

of 100 mg, 10-30 % of allergic patients showing symptoms at this dose. With exception of one anecdotic report in the year 1963 there are no hints for unequivocal clinical reactions with an oral dose of less than 1 mg (Hourihane, 2001).

Investigations on threshold doses for induction of a new food allergy have not been performed for ethical and safety reasons. Data by de Montis et al. (1993) point to a possible induction of allergies by consumption of plant oils in vitamin preparations.

Supposing the highest detected protein content of 2.7 % the minimal trigger dose of 100 µg protein may be reached with the ingestion of 4 mg lecithin. Soya lecithin is used as additive in oral forms mostly in amounts of 5-10 mg/dose, less usually in amounts of up to 50 mg. This means that the allergen quantity triggering minimal subjective reactions may be reached with a single dose unit. With application of larger amounts stronger clinically relevant reactions cannot be excluded.

With a maximal protein content of 10 mg/L in refined plant oils, which have passed through all refining steps including deodorization (heating to 230-250°C for 45-50 min) for a dose of 100 µg protein, the intake of at least 10 g oil is necessary. Soya and peanut oil are used as additives in oral forms in amounts of 50-300 mg/dose unit, which makes allergic reactions very unlikely, as confirmed by clinical experience. Nevertheless, the available studies show that the manufacturing processes are very inhomogeneous with respect to residual protein content. For this reason a general denial of risks is not acceptable.

Parenteral forms may contain much larger quantities of plant oils (e.g. 30-200 g/unit), andadministration of a relevant allergen dose may thus be expected regularly. Furthermore, no experience on intravenous threshold doses for induction of allergic reactions is available.

For topical preparations data on threshold concentrations for induction of a protein contact dermatitis are not available. A maximal exposition cannot be defined since the treated area varies strongly and may include the whole body surface.

Conclusion

Although relevant type I reactions have only been reported after intravenous infusion of major quantities of soya oil, soya and peanut products should be treated as allergenic unless they have an analytically-monitored non-allergenic specification and a safe maximum daily dose can be defined.

Skin rashes after use of soya oil /arachis oil baths may be interpreted as a protein contact dermatitis. Since no safe threshold for the exposition to topical oil preparations can be defined, and data point to the possibility of allergy induction due to the use of oil containing ointments in infants, all medications for topical use containing soya or peanut products should be treated as allergenic.

In oral preparations the administered amounts of soya/peanut are relatively small; large experience on standardised oral allergen provocations is available. The definition of a threshold level for total protein content in oral preparations may thus be useful. Mueller et al. (1998) found that the IgE binding potential of soya lecithin correlated with the total protein content. With a protein content of less than 20 ppb (ELISA) no specific IgE-binding could be demonstrated. Furthermore, in view of the clinical data a proven maximum daily oral intake of 20 µg protein should be tolerated without risk of major acute clinical reactions. The necessity of label warnings for products complying with these conditions must be discussed.

On the other hand, it must be kept in mind that with chronic oral consumption of oil-based formulas (e.g. vitamin D preparation in infants) containing only traces of protein, the induction of new allergies cannot be excluded. For soya and peanut containing medications used in children a general label warning irrespective of the protein content should be discussed.

Since available data point to cross-reactions, contra-indications for patients with known allergies to other legumes should be included.

Proposed formulations:

Product	Route of Adminis-tration	Threshold	Information for the Package Leaflet (for active compounds and excipients)		Reported adverse events in Germany for preparations with active compound (no reports for excipients)
			Contraindications	Side effects	
Arachis oil (peanut oil)	i.v.	zero	(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	In rare cases, anaphylactic reactions with hypotension may occur after intravenous application of medicinal products containing peanut oil.	none
	p.o.	with specified peanut protein content: max. daily dose 20 µg protein In all other cases: zero.	(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	Crude peanut oil is known to cause allergic reactions including severe anaphylaxis in persons with peanut allergy.	none
	topical		(Medicinal product) contains arachis oil (peanut oil). If you are allergic to peanut or soya, do not use this medicinal product.	In rare cases, skin rashes may occur after use of preparations containing soya oil. Eye contact may cause keratitis and should be avoided.	8 AEs related to peanut oil baths: keratitis / conjunctivitis due to eye contact (n = 7) eczema (n = 1)

Soya oil	i.v.	zero	(Medicinal product) contains soya oil. If you are allergic to soya or peanut, do not use this medicinal product.	In rare cases, fever and anaphylactic reactions with hypotension may occur after intravenous application of medicinal products containing soya oil. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya oil.	37 AEs related to infusion of large amounts of lipid emulsions. fever: n = 27 fever + exanthema: n = 2 exanthema: n = 1 abdominal pain: n = 3 diarrhoea: n = 1 hepatitis: n = 1 myocardial ischemia: n = 1 pleural effusion: n = 1
	p.o.	with specified soya protein content: Max. daily dose 20 µg protein In all other cases: zero.	(Medicinal product) contains soya oil. If you are allergic to soya or peanut, do not use this medicinal product.	Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.	None
	Topical	zero	(Medicinal product) contains soya oil. If you are allergic to soya or peanut, do not use this medicinal product.	In rare cases, skin rashes may occur after use of preparations containing soya oil. Eye contact may cause keratitis and should be avoided.	Skin rash: n = 4 Keratitis: n = 2

Soya lecithin	i.v. (rectal, inhalation)	zero	(Medicinal product) contains soya lecithin. If you are allergic to soya or peanut, do not use this medicinal product.	In rare cases, anaphylactic reactions may occur after intravenous application of medicinal products containing soya lecithin. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.	None (Anaphylactic reactions are reported for i.v. preparations containing soya lecithin as excipient, e.g. propofol.)
	p.o.	with specified soya protein content: Max. daily dose 20 µg protein In all other cases: zero.	(Medicinal product) contains soya lecithin. If you are allergic to soya or peanut, do not use this medicinal product.	Dietary soya-products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations.	none
	Topical	(not relevant)		(not relevant)	none

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