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Hypersensitivity Reaction to Generic Drug-Containing Soybean Oil

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1. Introduction

Over the last years the use of generic drugs has increased in the European Union due to their minor economic cost. The main regulatory request to market these products is their equivalence to the original compounds.

We describe two women that presented anaphylaxis after intake of generic omeprazole. The two patients had previously tolerated original non-generic omeprazole. Dot-blot assay revealed that the serum of the two patients was positive to generic omeprazole and soy.

The diagnosis of soy allergy should not be excluded in cases of drug hypersensitivity. We suggest to tests soy in all hypersensitivity reaction to generic drugs.

2. Brief report

Over the last years the use of generic drugs has increased in Spain and in the European Union due to their minor economic cost. The main regulatory request to market these products is their equivalence to the original compounds.

Soy bean is an additive of some drugs. Hypersensitivity reactions to soy bean oil as a result of drug intake have been scarcely reported¹⁻³. Recent studies on analytic investigation on protein content in refined seed oils suggest that fully refined seed oils should be taken into account in the context of allergic reactions and would benefit of further toxicological studies⁴.

We describe two women (58 and 81 years old) previously diagnosed of allergic asthma due to pollen, that presented a severe drug reaction (asthma, angioedema, hypotension), few minutes after intake of a capsule of a generic omeprazole. The two patients have been previously tolerated non-generic omeprazole.

After informed consent the following tests were carried out:

Patient 1: Skin prick tests (SPT) and ImmunoCAP assay (Phadia, Uppsala, Sweden) were positive with *Lolium perenne* and soy bean in the first woman (wheal mean diameter

with soy extract 20 mm, specific IgE to soy 9.01 KU/L) and with a dilution 1/10 in saline 0.9% of the powder contained in a capsule of the generic omeprazole (wheal mean diameter 14 mm).

Patient 2: This woman, previously diagnosed as asthmatic asthma due to grass pollen and oral syndrome after eating lentils, presented a wheal mean diameter with soy extract of 16 mm and a specific IgE to soy of 23 KU/L. SPT with omeprazole extract gave a wheal mean diameter of 12 mm. A positive control (histamine, 10 mg/mL) and a negative control (saline 0.9%) were also used.

SPT performed with non-generic omeprazole were negative. SPT performed with generic omeprazole extract were positive in other five patients sensitized to soy bean (wheal mean diameter 10 mm).

IgE-Dot Blot (Bio Rad, California, USA) assay was performed with the powder contained in a capsule of the generic omeprazole A and a capsule of generic omeprazole B reconstituted in 600 μ L of 20% ethanol/water (v/v), and extract of soybean (4 mg/mL of protein). The assay revealed as the serum of the two patients, was positive to generic omeprazole (A and B) and soybean extract but negative to diluents' wells, and the same samples was negative against the serum of a non-atopic patient. (Figure 1)

Although incidences of anaphylactic reactions induced by proton pump inhibitors of H2 are rare, they can be life threatening. Skin prick tests and oral challenge tests may be useful for the diagnosis, but immunological tests never confirm the presence of specific IgE antibodies to active principles of these drugs^{5,6}.

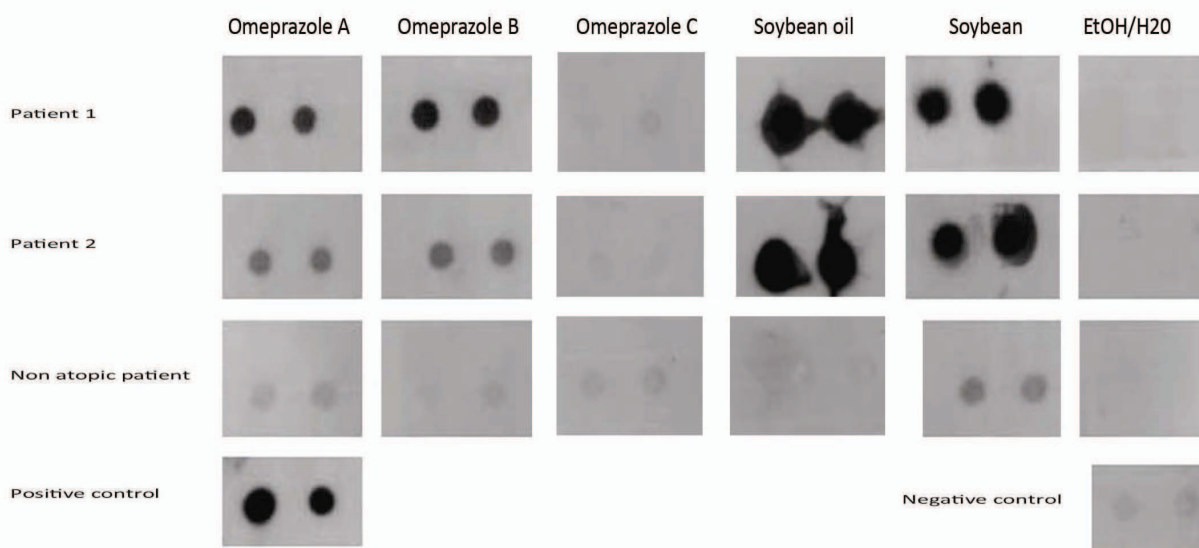


Fig. 1. Responses of serum from Patients 1 and 2 and from a nonatopic patient to generic omeprazole from two different manufacturers, to nongeneric omeprazole, to soybean oil, to soybean extract, and to diluents are shown. The response to *Dermatophagoides pteronyssinus* of serum from a patient who was sensitized to *D. pteronyssinus* extract, which was used as a positive control of the assay, is also shown.

Our observation suggests that an immediate hypersensitivity to drug-containing soy oil may cause anaphylaxis reaction in patients previously sensitized to this legume. The first report of possible anaphylaxis after a drug containing soybean oil implicated the drug propofol². Since propofol contains both egg lecithin and soybean oil, its use is contraindicated in patients with hypersensitivities to these component. Several other drugs may have a food component, resulting in contraindications and warnings in product labelling.

Several commercially important refined vegetable oils are derived from plants which are recognized as potent food allergens (peanut, soy). Full refining of oils results in the almost complete removal from oils of protein, which is responsible for allergic reactions. However, it is uncertain whether the minute amounts remaining could provoke allergic reactions in highly susceptible individuals. This has led to a vigorous debate about the safety of refined oils and specifically whether to label each oil individually because of the potential risk of allergenicity⁷.

Until active principles are clearly indicated in drug labellings, excipients and other minor additives are not included and only defined as excip. c.s. Since the introduction of generic drugs to the pharmaceutical market a debate exists whether they are well-investigated and of high quality. There is some uncertainty about whether evidence of bioequivalence is enough to guarantee efficacy and safety of generic drugs⁸. Food allergy consumers depend on ingredient labels for allergen avoidance⁹. However the drug labelling may not indicate the form or source of the allergen, and individuals who currently avoids foods may presented severe allergic symptoms after intake of drugs with minimal protein content such as soy oil, soy lecithin or lysozyme¹⁰. There are now reliable assays for the determination of soybean proteins in processed foods that may be applicable in drugs¹¹.

Soy is a clinical relevant allergenic source. The diagnosis of soy allergy should not be excluded in cases of drug hypersensitivity. We suggest to tests soy in all hypersensitivity reaction to generic drugs.

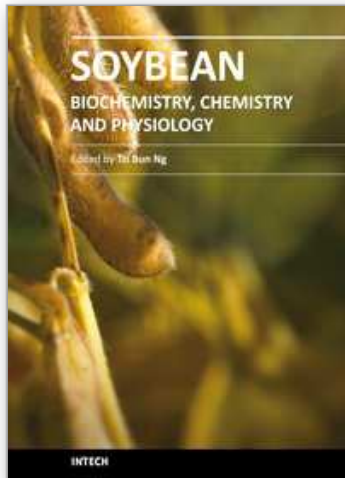
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Soybean is an agricultural crop of tremendous economic importance. Soybean and food items derived from it form dietary components of numerous people, especially those living in the Orient. The health benefits of soybean have attracted the attention of nutritionists as well as common people.

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