Letter to the Editor

# Anaphylaxis by antihistamine containing bovine gelatin: the utility of the basophil activation test in the diagnostic work-up

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Gelatin, a collagen protein obtained from cow and pig bones and fish skin is widely used, by the hydrolysis of collagen, in food preparations (sweets, yoghurt, etc.) and as a stabilizer in the pharmaceutical industry. In particular it could be found as an ingredient of drug capsules, plasma expanders, vaccines and plasma substitutes.

Systemic allergic reactions to gelatin-containing vaccines and drugs have been proven by anti-gelatin IgE assay [1–3] and by the Basophil Activation Test (BAT) [4].

Bovine gelatin sensitization is commonly associated with cow milk allergy and beef allergy [5].

We report the case of a 14-year-old patient affected by cow's milk allergy, who experienced lip paraesthesia, generalized itching and dyspnoea with bronchospasm after the ingestion of lyophilised ebastine; the reaction was handled in the emergency room with intramuscular and aerosolized epinephrine, systemic corticosteroids and antihistamines.

The clinical history revealed an asthmatic reaction after polio vaccination and an egg allergy; for this reason the patient did not undergo any other immunization.

Since the information leaflet of ebastine showed the presence of gelatin as an ingredient of the lyophilised drug, we suspected a bovine gelatin hypersensitivity.

We did not perform either the skin prick test with bovine gelatine and ebastine (kindly provided by the drug manufacturer) or the oral challenge test with ebastine because the patient had previously experienced an anaphylactic reaction after the skin prick test with a commercial extract of milk.

Specific IgE (ImmunoCap Phadia, Uppsala, Sweden) to bovine gelatin and beef was detected and we also carried out the basophil activation test with gelatin and ebastine in order to exclude or confirm hypersensitivity to the antihistamine. In our patient, specific IgE for gelatin and beef result was 0.01 kU/l and 0.10 kU/l, respectively.

Peripheral whole blood samples were collected in heparinized tubes: 100 µl of whole blood was pre-incubated with 20 µl of the basophil stimulation buffer (containing IL-3). Basophils from the patient and from five healthy controls were stimulated with 100 µl of the basophil stimulation buffer as negative control (BD Pharmingen) and with 100 µl (10 µg/ml) of anti-IgE as positive control (BD Pharmingen). Then we used, as stimulants, 100 µl of bovine gelatin contained in the drug and 100 µl of ebastine. The degranulation was stopped on ice, the cells were stained with CD63-FITC/CD123-PE/Anti-HLADR-PerCP (BD FastImmune) and the samples were lysed, fixed, washed and analyzed within 3 h on a FACS-Canto flow cytometer (BD, Immunocytometry Systems, San Jose, CA, USA). Activated basophils were gated as CD123+/HLADR–/CD63+ and the results of BAT were expressed as a percentage of CD63+ basophils.

The basophil activation test with gelatine and ebastine resulted in no activation of cells in any of the five healthy controls, while a dose-dependent CD63 up-regulation (from 67% to 87%) was observed in the patient after the stimulation with gelatine. No basophil activation was observed after ebastine stimulation.

In the literature, Apostolou *et al.* [4] reported a sensitivity of 100% and a specificity of 87.5% of the basophil activation test for the diagnosis of Gelofusine allergy.

Hypersensitivity to gelatin can be diagnosed by the detection of the specific IgE and skin prick test, however BAT could be an additional test [6] in fact, even if the skin prick test remains "the gold standard" for the diagnosis of a drug hypersensitivity, our case report is an example

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of the utility of the BAT in the diagnostic work-up of a patient who experienced a history of anaphylaxis during the skin prick test with other allergens.

In conclusion, we suggest that BAT should be considered a safe *in vitro* test especially when *in vivo* tests are contraindicated. Moreover it is important to underline that the type of gelatin used as ingredients of drugs should be specified in the information leaflet in order to avoid hypersensitivity reactions in potential allergic patients.

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Eleonora Nucera, Amira Colagiovanni and Domenico Schiavino – equally contributed.

## Conflict of interest

The authors declare no conflict of interest.

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