Anaphylaxis case report to trimethylphloroglucinol (Spasfon®)

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Letter to the Editor

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Dear Editor,

Phloroglucinol (P) and its methylated derivative (TMP) are both phenol derivative antispasmodic agents (Fig. 1) acting on smooth muscle and prescribed to treat acute spasmodic abdominal pain, acute painful disorders of the urinary tract, and acute pain in gynecology. It has been showed that P and TMP act by reducing glycerol-induced abdominal pain and by inhibiting colonic phasic contractions.[1]

Exceptionally, P and TMP are associated with muco-cutaneous manifestations and allergic reactions. It has been reported, in the French National pharmacovigilance database, 21 cases of anaphylaxis to phloroglucinol, including 16 cases of anaphylactic shock and 5 cases of allergic skin reaction (unpublished data).

We report a case of anaphylaxis to phloroglucinol confirmed by skin testing.

Case report

We report the case of a 23 year old female patient, who has a medical history of mildly active ulcerative colitis treated with mesalamine (Pentasa®). She had no relevant past surgical history. The patient was evaluated in allergy consultation for a recent generalized facial maculo-papular exanthema associated with dysphonia, dysphagia and mild dyspnea that occurred 6 months ago. In fact, this systemic reaction appeared half an hour after taking Spasfon®, paracetamol, loperamide and a cough syrup containing codeine (Polery®), during an influenza-like illness with gastroenteritis. She then presented to the emergency department where she was given intravenous H1 antihistamine plus a single intravenous corticosteroid dose (methylprednisolone 1 mg/kg). Dysphonia, dysphagia and dyspnea improved successfully and she was discharged on oral antihistamine and corticosteroid for 5 days. The facial skin eruption disappeared slowly over 3–4 days.

All drugs that have been taken are known to cause allergic reactions as side effects. Also, children and adult can commonly develop urticaria as a result of viral respiratory infections.[2]

As this systemic reaction can evoke an immunological IgE mediated mechanism, we decided to test all drugs that were taken on that day. An allergic food reaction is unlikely, given the absence of food intake for at least 6 h before the reaction, and the absence of ingestion of unusual foods within the 24 h before the reaction.

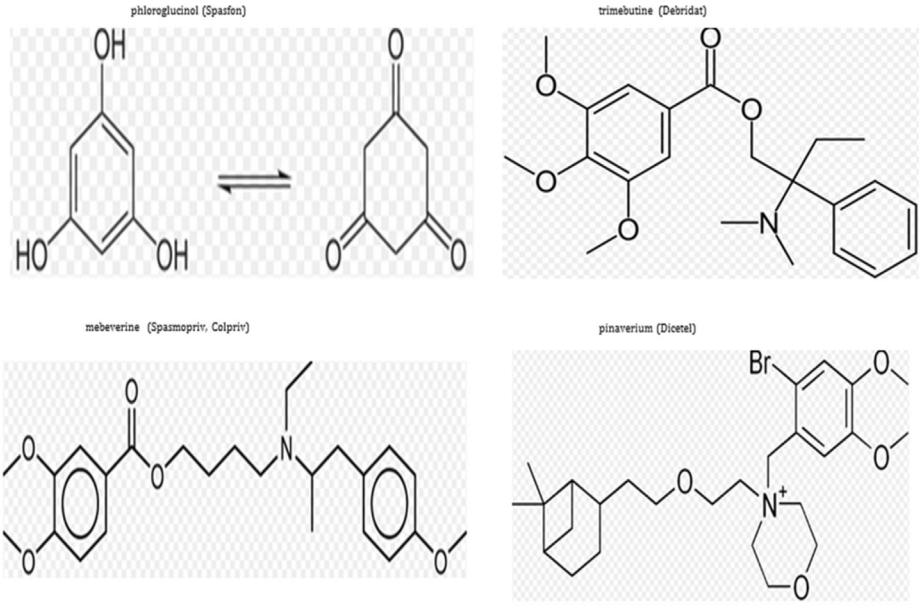

Fig. 1. From left to right, and up to down: phloroglucinol, trimebutine, mebeverine, pinaverium.

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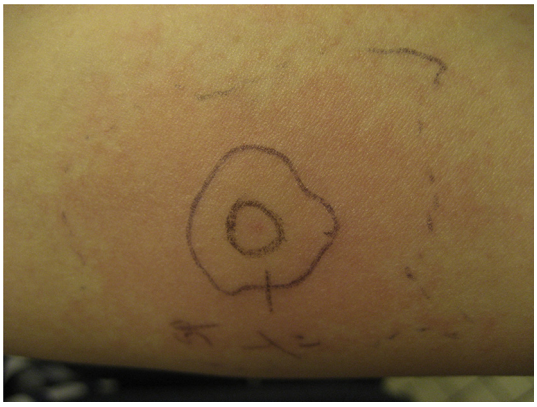

Fig. 2. Intradermal test to Spasfon at concentration 1 mg/ml.

Since this reaction, paracetamol was reintroduced by the patient without allergic symptoms and mesalamine (Pentasa®) was continued on a daily based treatment with good tolerance. Skin prick tests were initially done for Spasfon®, loperamide and Polery®, and were strongly positive for Spasfon® and negative for the others.

In fact, for skin prick testing, a 80 mg tablet of Spasfon® was crushed in 1 ml of NaCl 0.9%, and turned out positive at 80 mg/ml and 8 mg/ml. The skin tests were repeated by using the injectable solution of Spasfon® that only contains the active ingredient phloroglucinol and NaCl. Prick tests were positive at 10 mg/ml (with a mean weal diameter of 7 mm after 15 min compared to a positive histamine control of 5 mm and a negative saline control test). Intradermal tests at 10 mg/ml and 1 mg/ml were also positive (with a mean initial wheal of 8 mm increasing to 40 mm 20 min later surrounded by an erythema of 115 mm diameter at a skin testing concentration of 1 mg/ml) (Fig. 2).

Single blinded challenge tests were performed for all the other simultaneously ingested drugs and all turned out negative. Thereby, skin tests and oral negative challenge tests, lead us to conclude to an allergic reaction, IgE mediated, to trimethylphloroglucinol (Spasfon®) explaining the systemic reaction presented by the patient.

From a pharmaco-chemical point of view, the TMPs is a phenol derivative with antispasmodic properties that predisposes to cross reactivity with other molecules such as paracetamol and other antispasmodic such as pinaverium (Dicetel®), mebeverine (Spasmopriv® or Colopriv®) and trimebutine (Debridat®).

Given the past medical history of a chronic digestive disease requiring frequent recourse to antispasmodics, finding a therapeutic alternative was needed. We did an oral challenge test to trimebutine, which was found to be negative.

Discussion

To our knowledge, no cases of documented immediate hypersensitivity reactions to Spasfon® have been reported in the literature in full details. Only one, amongst a list of 333 drug induced anaphylaxis from the French Allergy Vigilance Network.[3] The only information for this case is the positivity of skin prick test, as for our patient.

In the case of our patient, the clinical history of facial skin eruption, dyspnea, dysphonia and dysphagia, occurring 30 min after drug intake, was compatible with an immediate, possibly IgE dependent allergic reaction.

Due to the severity of the episode, skin and oral challenge tests were done for all possible drugs involved. Prick test to Spasfon® was the only positive test at a concentration of 80 mg/ml and 8 mg/ml. Since no standardized dosage is known for skin testing to this drug, ten healthy controls were tested and were all negative. We validated the positivity for the active ingredient, and not the excipients, by carrying out prick tests using the injectable solution.

A total of twenty-one cases of anaphylaxis, out of which 16 with anaphylactic shock, following ingestion of Spasfon® have been declared to the French National Pharmacovigilance Database. Allergy work-up was performed only in 2 cases, including our patient, and the patient declared to the French Allergy Vigilance Network,[3] both had a positive prick test to Spasfon® (unpublished data).

Although exceptional, allergic reactions to phloroglucinol and trimethylphloroglucinol need to be confirmed or infirmed whenever they were part of the therapeutic arsenal. The multiple available drugs with “benzene ring” in their chemical structure require searching for possible cross reactivity with other similar products.

Conflict of interest

The authors have no conflict of interest to declare.

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