

Anaphylactic reaction to povidone secondary to drug ingestion in a young child

To the Editor,

Povidone (PVP, polyvinylpyrrolidone) is a mixture of synthetic polymers with molecular weights (between 10,000 and 70,000 Da) comparable to those of the plasma proteins. It is commonly used as an excipient in different pharmaceutical products; in artificial tears and contact lens preservation solutions; as an additive in foodstuffs (E-1202), serving as a support for edulcorants, and in food supplements in the form of tablets and pills; as an antiseptic (Betadine®); and as a dispersant and stabiliser in hair sprays. Contact dermatitis associated to povidone-iodine is not rare, though immediate hypersensitivity reactions to this substance are unusual, with few cases of anaphylaxis documented in the literature. We present a case of anaphylactic reaction in a young boy.

A boy aged four years and two months was seen for the study of asthma beginning at one and a half years of age. The patient had suffered an episode of asthma and rhinitis at the age of three years and 10 months, developing 1–2 h after receiving Estilsona® (prednisolone oral solution), perioral and nasogenian swelling and erythema, and eye itching with conjunctival reddening. The condition lasted 4–6 h, and no other manifestations were described. The patient had taken this medication several times before without reactions.

Initial exploration based on the prick test revealed the following: *Dermatophagoides farinae* and *D. pteronyssinus* 4+, grass pollen 2–3+, dog epithelia 3+, and cat dander 2–3+ (with respect to histamine). Estilsona® (13.3 and 1.33 mg/ml of methylprednisolone stearate): 3 × 2 mm (2+), with histamine 4 × 3 mm. Budesonide suspension for nebulisation (250 µg/ml) and methylprednisolone (solution for injections) 10 mg/ml and 1 mg/ml, negative. An open oral provocation test with the suspect drug (Estilsona®) was performed: after a cumulative dose of 0.5 ml containing 6.65 mg of prednisolone stearate, equivalent to 3.5 mg of prednisolone (first 0.2 ml and then 0.3 ml after 30 min), and equivalent to a quarter of the therapeutic dose of prednisolone calculated as 1 mg/kg b.w., perioral erythema and wheals developed after 20 min. The dosage was repeated half an hour after the previous dose, and 10 min later the patient developed intense barking cough with mild dyspnoea, watery rhinorrhea, sneezing, some wheals on the face and arms, and inspiratory and expiratory wheezing. Intramuscular adrenalin was therefore administered, with inhalatory salbutamol, levocetirizine and a single dose of deflazacort via the oral route. Half an hour later the respiratory symptoms disappeared, while the nasal symptoms and urticaria were resolved after 2 h.

One month later the study was amplified, testing all the components and excipients:

Prick test and intradermoreaction negative to methylprednisolone (10 and 1 mg/ml), betamethasone (4 and

0.4 mg/ml) and hydrocortisone (20 and 2 mg/ml), and to 20% mannitol (1/100 and 1/10 dilutions).

Prick test negative to Tween 80 (polysorbate), without dilution and diluted 1/10.

Prick test with betadine solution: without dilution: 6 × 4 mm, diluted 1/10: 11 × 6.5 mm. Histamine: 5 × 5 mm. Negative control in the mother and in another child. Prick test with pure non-iodinated povidone (2.5%) (25 mg/ml): 6 × 6 mm, histamine: 4 × 4.5 mm (Fig. 1).

Provocation testing was carried out with methylprednisolone in tablets to a total of 20 mg, with negative results.

In order to determine whether specific IgE against PVP could be detected in the serum of the patient, we applied the dot-blot technique, using two different membranes: nitrocellulose and PVDF (polyvinylidene fluoride)¹, with negative results in both cases. ELISA likewise² proved unable to identify such antibodies.

One month after completing the diagnosis, and despite the recommendations given to the family and patient physician, the boy by mistake received Zinnat® sachets 250 mg (cefuroxime axetyl and povidone K30). One hour after the first dose, he developed nasogenian swelling, pharyngeal itching, barking cough with slight breathing difficulties, mild wheezing, rhinorrhea, sneezing in salvoes and left eyelid oedema. Salbutamol was provided, together with hydroxyzine and deflazacort, after which the clinical manifestations disappeared within 2 h.

Immediate (type 1) hypersensitivity reactions to povidone (PVP) are very infrequent, and only three cases in children have been published to date (all of them presenting anaphylactic reaction). In our case the patient was younger (3 years and 10 months) than the other published paediatric cases and suffered a mild anaphylactic reaction. In the first of these three cases, the reaction was presented to the eight and a half-year old after the ingestion of flubendazol (containing PVP), and at nine years of age, by cutaneous application of Betadine®, being the skin tests positive, in the same way as in our patient, for the drug responsible and for the PVP. The conjunctival provocation test with flubendazole proved strongly positive.³ The second case corresponded to a nine-year-old boy who developed urticaria, rhinoconjunctivitis and dyspnoea half an hour after ingesting a formulation containing paracetamol. This patient had previously suffered erythema and itching of the scalp after the application of a hair conditioner, as well as urticarial reactions with penicillin and fluoride tablets. The substance common to all these products was PVP, which yielded a positive prick test.⁴ The authors of this publication pointed out that the reported cases are grouped within the last 10 years, despite the fact that PVP has been in use for longer; as a result, there may be other, undiagnosed cases of this same kind of problem. The last reported case corresponds to a boy with atopic dermatitis who developed an anaphylactic reaction after applying povidone-iodine for impetigo, on two occasions (at seven and nine years of age). The skin tests proved negative, and the diagnosis was



Fig. 1 Prick test: Histamine (Control). Negative control in the mother and in another child. Prick test with pure non-iodinated povidone (2.5%) (25 mg/ml): 6 × 6 mm, histamine: 4 × 4.5 mm.

confirmed by means of a histamine release test involving stimulation with PVP.⁵

The rest of the cases documented in the literature correspond to adults:

- Two cases involving the intraarticular administration of drugs containing corticosteroid and PVP, with a positive provocation test to the latter and a positive intracutaneous test to PVP in one of the cases⁶, while intramuscular provocation (1 ml) with PVP proved positive in the other patient.⁷
- Four cases involving the topical use of povidone-iodine. One patient developed urticaria and angio-oedema secondary to Betadine[®] application on an arm wound, with confirmation at prick testing with Betadine[®] and PVP, and demonstrating specific IgE against PVP.⁷ Another two patients developed severe anaphylactic reactions after applying Betadine[®] to surgical wounds.^{8,9} One of them, described by the reporting authors as the first documented case of anaphylaxis to povidone-iodine, yielded positive skin tests to Betadine[®] and PVP, while basophil activation and leukotriene release testing proved positive for Betadine[®].⁸ The other patient presented a positive prick test for povidone-iodine.⁹ Lastly, a case of anaphylaxis following the vaginal administration of povidone-iodine has been reported, with a positive prick test and positive histamine release test in response to PVP-K60.¹⁰
- A reaction in the form of bronchospasm has been described 2 h after the administration of contrast medium containing PVP, with positive intradermal tests and histamine release findings in response to PVP and povidone-iodine.
- Finally, a case has been reported likewise involving anaphylaxis following analgesic administration in tablet form, with a positive scratch test to PVP, a positive lymphocyte transformation test, and the presence of specific IgE as established by the dot-blot technique.¹

In our patient, the skin tests were clearly positive to the drug (Estilsona[®]), to povidone-iodine, and to pure PVP, even though specific IgE against PVP could not be demonstrated by two of the techniques used in some of the commented cases.^{1,2} Ours is the only case confirmed through oral provocation, although in two of the mentioned cases provocation testing was carried out (intramuscular in one case and conjunctival in the other). Provocation testing was decided on for a number of reasons: prick test positivity (Estilsona[®]) was not intense; the clinical picture was added to the manifestations inherent to the respiratory allergic condition of the patient, without being able to directly attribute the symptoms (which in any case corresponded to a mild allergic reaction) to the drug product; and allergic reactions to drugs of this kind are infrequent, particularly in such young children.

Although very few paediatric cases have been reported (only four, including our own patient), it is noteworthy that all of them were characterised by the presence of atopic disease: atopic dermatitis,^{3,5} allergic rhinoconjunctivitis,^{3,4} and asthma and allergic rhinitis in our patient. This possibly suggests that atopic disease could constitute a risk factor for hypersensitivity to PVP.

In conclusion, we have presented the youngest case published to date of an anaphylactic reaction secondary to the ingestion of povidone in drugs that contain this substance in their formulation. Cases such as ours, while exceptional, point to the need to also take drug excipients or preservatives into account as possible causes of immediate hypersensitivity reactions to drugs, and not only the active ingredient. An early diagnosis is particularly important when widely used products are implicated, as in our case, and potentially serious anaphylactic reactions are involved. Avoidance in such situations should be complete and strict, with due consideration of the possibility of accidental exposures, and self-administrable adrenalin should be on hand at all times.

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***Russula cutefracta* inhibits antigen-induced degranulation and Syk and MAPK phosphorylation in rat basophilic leukaemia cells**

To the Editor,

Russula cutefracta (synonymous with *Russula cyanoxanthus*) is a mushroom of the genus *Russula* commonly found in parts of Europe and Asia. Although species of *Russula* have rarely been used for medicinal preparations, extracts of other mushrooms species are used as traditional remedies for various diseases in Asian countries. Recent evidence indicates that the mushroom lectins, polysaccharides, and other molecules have general anti-tumour, anti-inflammatory, and immunomodulatory properties. Here, we investigated the effects of *R. cutefracta* on mast cell degranulation, an important step in allergic reactions.

Mast cells are important for immediate hypersensitivity and the inflammatory response and the rat basophilic leukaemia cell line, RBL-2H3, has proven useful for studying the biology of mast cells.¹ Allergy, or immediate (Type I) hypersensitivity, is one of four types of hypersensitivity.² The binding of antigen to the high affinity IgE receptor (FcεRI) on the surface of mast cells and basophils induces the release of histamine, prostaglandin, arachidonic acid metabolites, proteases, heparin sulphate, serotonin, leukotrienes, and proinflammatory cytokines from secretory vesicles called granules.^{3,4}

Basophils and mast cells express high levels of FcεRI consisting of an α chain, a β chain, and two disulfide-linked γ chains.^{3,4} The α chain of FcεRI contributes to high affinity IgE binding whereas the β and γ chains, which contain immunoreceptor tyrosine-based activation motifs (ITAMs), initiate the downstream signalling cascade leading to release of preformed and newly synthesised mediators.^{3,4} The spleen tyrosine kinase (Syk) plays an essential role in the IgE-dependent activation of mast cells. For example, cross-linking of FcεRI results in phosphorylation of the ITAMs on the β and γ chains by Lyn, a Src family kinase.⁵ The phosphorylated γ chains then bind and activate Syk, which has an essential role for FcεRI-proximal signalling pathways.^{6,7} However, many more kinases including Fyn, PI3-kinase,

PLC-γ, and MAPKs are important for mast cell activation and degranulation.^{3,4} Therefore, the inhibition of these kinases by natural compounds found in *R. cutefracta* might suppress the release of hypersensitivity-inducing mediators in mast cells, thereby leading to inhibition of the allergic response.

As a first step toward using *R. cutefracta* as a treatment for allergy, dried *R. cutefracta* (80 g) was used to prepare *R. cutefracta* extract (RCE) by three extractions with ethanol. After filtration, excess water was removed with a rotary evaporator under vacuum at 50 °C. Next, we determined whether RCE is toxic by assessing the viability of mast cells. RBL-2H3 cells were treated with various concentrations of RCE for 12 h and cell viability was determined by MTT assay. Untreated cells were used as a negative control (Fig. 1A). We did not observe any increase in cell death due to RCE, although we tested a range of concentrations from 10 μg/ml to 100 μg/ml (Fig. 1A). Therefore, in the range of concentrations used in our study, RCE was not toxic to mast cells.

Mast cell degranulation is a cellular process whereby secretory vesicles release hypersensitivity-inducing molecules including histamine, proteoglycans and proteases. β-Hexosaminidase is another molecule present within mast cell granules and this marker has been used widely to monitor degranulation.⁸ Mast cells were incubated with DNP-specific IgE (20 ng/ml) overnight and various concentrations of RCE (10 μg/ml, 20 μg/ml, and 100 μg/ml) for 30 min, resulting in a dose-dependent decrease in degranulation, as measured by β-hexosaminidase release (Fig. 1B). In comparison, our control experiments with untreated cells or cells receiving antigen stimulation only resulted in no degranulation and complete degranulation, respectively (Fig. 1B). Another control experiment using PP2 (10 μM), a general Src-family kinase inhibitor, also inhibited degranulation and RCE at 30 μg/ml and 100 μg/ml were as potent as PP2 in inhibiting degranulation (Fig. 1B). We believe that this is the first demonstration of the anti-allergy properties of *R. cutefracta*.

An increase in cytosolic Ca²⁺ ionophore concentration ([Ca²⁺]_i) is thought to be important for mast cell degranulation.⁹ Also, it is known that thapsigargin, a potent inhibitor of Ca²⁺-ATPase in the endoplasmic reticulum membrane and ionomycin, a Ca²⁺ ionophore, cause mast cell degranulation without FcεRI activation.¹⁰ To determine whether degranulation resulting from an increase in