

Rectal Drug formulations´ induced anaphylaxis

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Anaphylaxis after enema administrations has been described as a latex allergy manifestation during diagnostic procedures and exceptionally due to other allergens. Most of them have been severe episodes, including fatalities [1-5].

Rectal drug formulations (RDF) allow performing diagnostic procedures and treating local and systemic diseases. Available drugs include antipyretics, benzodiazepines, laxatives and mesalazine [6]. Clinical trials on other drugs such as antibiotics, vaccines or faecal microbiota are in process [6].

We describe two patients with anaphylaxis after honey-based enemas administration, review similar cases and elucidate on possible implied mechanisms.

Case 1

One 6-year old child developed acute abdominal pain, abundant diarrhoea, limpness, generalized erythema and dyspnoea 15 minutes after the first administration of Melilax pediatric®, a commercially available honey-based enema. Generalized urticaria, facial oedema and slowed capillary refill (Blood Pressure (BP): 95/55 mmHg; Heart Rate (HR): 90 bpm; Oxygen

saturation: 98% at ambient air) were detected at the Emergency Department. Symptoms resolved after epinephrine (0.15 mg), dexchlorpheniramine (2.5 mg) and methylprednisolone (20 mg) in 15 minutes. Tryptase measurement (30 minutes after symptoms' onset) was 5.3 mcg/L.

Parents denied foods or drugs ingestion prior to the onset of symptoms. He had tolerated previously honey and infusions and referred no prior rhinoconjunctivitis symptoms either.

Case 2

A 20-year-old woman developed immediate dyspnea, anal pruritus, facial edema, dizziness and hypotension (BP: 75/37 mmHg; HR: 59 bpm; Oxygen saturation: 91% at ambient air) after the administration of two rectal enemas (Melilax Adult®). She received dexchlorpheniramine (5 mg) and methylprednisolone (40 mg). Tryptase was not determined. This patient had previous anaphylaxis: One after kiwi and another after a Polyethylene glycol containing laxative ingestion, respectively. She also referred contact urticaria episodes after *compositae* pollen exposure and seasonal rhinoconjunctivitis. She had been advised to avoid honey ingestion.

Allergy work-up consisted of skin prick tests (SPT) with honey, *compositae* pollens, the enema as is and its individual components, provided by the manufacturer. Additional skin tests included a battery of common inhalants and foods. Specific IgE determinations and an ImmunoCAP ISAC sIgE 112 (ImmunoCAP Thermo Fisher Scientific, Uppsala Sweden) were also performed.

Both patients' had positive skin and in vitro tests with honey and *compositae* pollens. Skin tests with enema components including honey and honeydew were also positive (Full allergy work-up detailed in supplementary file).

Skin tests with Melilax® in 10 healthy controls were negative.

Anaphylaxis after RDF is infrequent. Published data include case reports or small series. Latex was the most frequent elicitor but other allergens, including homemade chamomile infusion enemas have also been described. Patients of all ages have been affected. Most of them developed severe episodes, including cardiovascular and neurologic symptoms [1-5]. Rectal exposure route's role as a possible severity factor has not been discussed.

RDF allows giving certain drugs in emergencies or poor oral tolerance. It is considered an appropriate administration route at any age except preterm or in immunocompromised patients [6]. Rectum has a very limited role in water and electrolytes absorption. Specific features that influence drug administration and absorption include: a limited liquid and microbiome content, which do not degrade drugs; absence of villi or microvilli with a limited mucosal surface for absorption and a drainage system that avoids partially the portal system. Inferior and middle rectal veins drain to the inferior vena cava. Local lymphatic system also avoids the hepatic first-pass effect. Besides, drug related factors, such as the drug itself or variations in formulations, such as suppositories, solutions or foams can influence its absorption [6]. Half of a RDF will bypass the liver avoiding hepatic first-pass effect. It may be an adequate option for drugs with important hepatic first-step metabolism, poor gastrointestinal absorption and/or easy degradation [6].

Digestive tract includes several immune elements: intestinal epithelial barrier, the lamina propria and the gut-associated lymphoid tissue (GALT) [7,8]. Besides, gut microbiota has a role in the development of GALT and in immune system regulation [7,8]. Gastrointestinal tract immune system's functions include tolerance development of dietary antigens and commensal flora [7,8]. Food allergy is a failure of tolerance acquisition.

Rectal mucosa may have a role in immune responses' development against pathogens, as suggested by research with vaccines for rectal administration [9]. However, it is structurally

and functionally different from other gastrointestinal tract compartments such as the ileum. For instance, novel studies suggest the importance of microvilli structure in tolerance development [8]. Such elements are absent in rectum [7]. Therefore, RDF avoids essential steps leading to food tolerance development: oral exposure itself; protein/allergen degradation during digestion; interaction with gut microbiota; epithelial barrier crossover and interaction with antigen presenting cells. It has also been implied that avoiding portal circulation may also impair oral tolerance acquisition [7,8].

Honey may have also played a role in the episodes' severity, considering its allergen contents and formulation factors such as viscosity and adherence. Honey consists of a complex mix of flowers nectars, honeydew, proteins and secretions of pharyngeal and salivary bee glands. Potential allergen sources include pollen proteins, bee body components, mold spores and other debris [10]. Primary sensitization may develop through airborne compositae sensitization, honey or other pollen-derived products ingestion, or due to bee stings [10]. Both patients were sensitized to *compositae*. The first might have been sensitized by honey and infusions' ingestion and the second through skin or airborne exposure. She had been advised against honey ingestion, but considered the enema being safe because she identified it as "something natural".

In conclusion, we present two patients with anaphylaxis after honey-based enemas administration. To our knowledge, there have been no prior reports of honey-based enema induced anaphylaxis. We consider rectal exposure may have influenced the symptom severity since it involves the rapid passage of large amounts of non-digested proteins and allergens to systemic circulation and avoids immune elements that facilitate tolerance. Besides, particularities in this enema formulation may have lengthened its retention, increasing allergen absorption.

Current list of RDFs is limited. This may change in the future. Besides, constipation is a common pathology frequently treated with complementary medicines, home remedies or non-prescription drugs, apparently benign but not risk-free.

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