

## Anaphylaxis Induced by Rectal Drug Formulations

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Anaphylaxis after administration of an enema has been described as a manifestation of latex allergy during diagnostic procedures and, exceptionally, as being due to other allergens. Most episodes were severe, and some even fatal [1-5].

Rectal drug formulations (RDFs) make it possible to perform diagnostic procedures and treat local and systemic diseases. Currently available drugs that can be administered rectally include antipyretics, benzodiazepines, laxatives, and mesalazine [6]. Clinical trials on other drugs such as antibiotics, vaccines, and fecal microbiota are in process [6].

We report 2 cases of anaphylaxis after administration of a honey-based enema, review similar cases, and discuss possible implicated mechanisms.

The first patient was a 6-year-old boy who developed acute abdominal pain, abundant diarrhea, limpness, generalized erythema, and dyspnea 15 minutes after the first administration of Melilax Pediatric, a commercially available honey-based enema. Generalized urticaria, facial edema, and delayed capillary refill (blood pressure, 95/55 mmHg; heart rate, 90 bpm; oxygen saturation, 98% on room air) were detected in the emergency department. Symptoms resolved 15 minutes after treatment with epinephrine (0.15 mg), dexchlorpheniramine (2.5 mg), and methylprednisolone (20 mg). The tryptase value was 5.3 µg/L 30 minutes after onset.

The parents denied ingestion of foods or drugs prior to the onset of symptoms. The patient had previously tolerated honey and infusions and reported no prior symptoms of rhinoconjunctivitis.

The second patient was a 20-year-old woman who developed immediate dyspnea, anal pruritus, facial edema, dizziness, and hypotension (blood pressure, 75/37 mmHg; heart rate, 59 bpm; oxygen saturation, 91% on room air) after administration of 2 rectal enemas (Melilax Adult). She received dexchlorpheniramine (5 mg) and methylprednisolone (40 mg). Tryptase was not determined. The patient had previously experienced anaphylaxis, once after eating kiwi and again after ingestion of a polyethylene glycol-containing laxative. She also reported contact urticaria episodes after exposure to

Compositae pollen and seasonal rhinoconjunctivitis. She had been advised to avoid ingestion of honey.

The allergy work-up consisted of skin prick tests with honey, Compositae pollens, the enema as is, and the individual components of the enema, which were provided by the manufacturer. Additional skin tests included a battery of common inhalants and foods. Specific IgE determinations and an ImmunoCAP ISAC sIgE 112 assay (ImmunoCAP, Thermo Fisher Scientific) were also performed.

Both patients had positive skin and in vitro test results with honey and Compositae pollens. Skin tests with the enema components, including honey and honeydew, were also positive (see Supplementary file for details of full allergy work-up).

Skin tests with Melilax in 10 healthy controls were negative.

Anaphylaxis after administration of RDFs is infrequent. Published data include case reports and small series. Latex was the most frequent elicitor, although other allergens, including homemade chamomile infusion enemas, have also been described. Patients of all ages are affected. Most developed severe episodes, including cardiovascular and neurologic symptoms [1-5]. The role of rectal exposure as a possible determinant of severity has not been discussed.

RDFs make it possible to administer certain drugs in emergencies or cases of poor oral tolerance. It is considered an appropriate administration route at any age, except in preterm neonates or in immunocompromised patients [6]. The rectum has a very limited role in water and electrolyte absorption. Specific features that influence drug administration and absorption include the following: limited liquid and microbiome content, thus preventing drug degradation; absence of villi and microvilli, thus leaving a limited mucosal surface for absorption; and a drainage system that partially avoids the portal system. The inferior and middle rectal veins drain to the inferior vena cava. In addition, the local lymphatic system enables the formulation to avoid the first-pass effect. Absorption can also be affected by the drug itself and variations in formulations (eg, suppositories, solutions, and foams) [6]. Half of an RDF will bypass the liver, thus avoiding the first-pass effect. This may be an adequate option for drugs with important first-pass metabolism, poor gastrointestinal absorption, and/or easy degradation [6].

The digestive tract includes several immune elements: the intestinal epithelial barrier, the lamina propria, and gut-associated lymphoid tissue (GALT) [7,8]. Gut microbiota also plays a role in the development of GALT and in immune system regulation [7,8]. The functions of the immune system in the gastrointestinal tract include development of tolerance to dietary antigens and commensal flora [7,8]. Food allergy can be considered a failure to acquire tolerance.

The rectal mucosa may have a role in the development of the immune response 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, recent studies suggest the importance of microvilli structure in development of tolerance [8]. Since such elements are absent in the rectum [7], RDFs avoid the essential steps

leading to development of food tolerance, namely, oral exposure, protein/allergen degradation during digestion, interaction with gut microbiota, epithelial barrier crossover, and interaction with antigen-presenting cells. Avoiding portal circulation may also impair oral acquisition of tolerance [7,8].

Honey may have played a role in the severity of the episodes we report, considering its allergen contents and formulation-related factors such as viscosity and adherence. Honey consists of a complex mix of flower nectars, honeydew, proteins, and secretions of bee pharyngeal and salivary glands. Potential allergen sources include pollen proteins, bee body components, mold spores, and other debris [10]. Primary sensitization may develop through sensitization to airborne Compositae, honey, or other pollen-derived products or as a result of bee stings [10]. Both patients were sensitized to Compositae. The first might have been sensitized as a result of ingesting honey and infusions, and the second through skin or airborne exposure. The patient had been advised against ingestion of honey but considered the enema to be safe because it was a natural product.

In conclusion, we present 2 cases of anaphylaxis after administration of a honey-based enema. To our knowledge, there have been no prior reports of anaphylaxis induced by a honey-based enema. We believe that rectal exposure may have influenced the severity of symptoms, since it involves the rapid passage of large amounts of nondigested proteins and allergens to the bloodstream and avoids immune elements that facilitate tolerance. Furthermore, specific aspects of the enema formulation reported may have lengthened its retention time, thus increasing allergen absorption.

The current list of RDFs is limited. This may change in the future. In addition, constipation is a common condition that is frequently treated with complementary medicines, home-made remedies, and nonprescription drugs that are apparently benign but not risk-free.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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