

R E V I E W

Allergic reactions to cow's milk proteins in medications in childhood

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Summary. *Introduction:* Cow's milk is a frequent trigger of allergic reactions in childhood. Cow's milk proteins can be present in pharmaceutical excipients. *Methods:* We have analyzed paediatric literature on allergic reactions to cow's milk proteins in medication, focusing on the different routes of administration (inhaled, parental and oral). *Results:* Dry-powder inhalers may contain lactose as excipient. Lactose can be rarely contaminated with milk proteins and it may induce allergic reactions in patients with cow's milk allergy. Case reports have described immediate hypersensitivity reactions to methylprednisolone sodium succinate 40 mg injection, a formulation that contains lactose as excipient. Some cases of anaphylaxis after receiving diphtheria-tetanus-pertussis vaccine injection in children allergic to milk have been reported. Cow's milk proteins can be detected also in oral polio vaccine, certain probiotics and lactulose syrup. *Conclusions:* We suggest caution in administration of pharmaceuticals containing milk allergens in children allergic to milk. (www.actabiomedica.it)

Key words: cow's milk allergy, drug allergy, probiotics, vaccine, skin prick test, anaphylaxis, patch test, challenge test, lactose

Introduction

Cow's milk is a frequent trigger of allergic reactions, including anaphylaxis, in childhood (1). Diagnosis of cow's milk allergy (CMA) is based on skin prick tests and measurement of serum IgE (2) while patch tests are useless (3) and oral challenge to cow's milk is the diagnostic gold standard (4). Patients with CMA have to make their best to avoid common food and non-food products containing offending proteins. However, this is not easy when cow's milk proteins are present in pharmaceutical excipients. The prevalence of reactions to cow's milk allergens in medications has not been investigated in sensitized patients. Generally, it appears to be low but rising. The purpose of this review is to provide an overview on the role of cow's milk proteins contained in pharmaceuticals as a cause of allergic reactions.

Inhaled milk allergens

Dry-powder inhalers (DPIs) may contain lactose as excipient. Lactose is a carbohydrate that should not be considered allergenic since it is free of milk proteins and it is safe in children with CMA (5). However, lactose contained in dry-powder inhalers can rarely be contaminated by milk proteins. It has been demonstrated that in children with CMA, inhalation of milk proteins may precipitate severe allergic reactions (6, 7). Accordingly, in children with asthma, anaphylaxis has been elicited by inhaling dry powder containing fluticasone/salmeterol (8) or lanimavir (9) and lactose contaminated with molecules of milk. Even if, in rare cases, milk allergen contamination of lactose-containing DPIs may induce allergic reactions in patients with CMA, patients allergic to milk usually do not have allergic reactions to lactose in DPI (10).

Parental route

Case reports have detailed immediate hypersensitivity reactions to methylprednisolone sodium succinate and diphtheria-tetanus-pertussis vaccine (DTP) in children with CMA.

Several children with high-level CMA have been reported to develop urticaria and anaphylaxis following intravenous methylprednisolone sodium succinate 40 mg injections that contain lactose as excipient (11-14). This methylprednisolone formulation with lactose may also contain milk proteins (15). In patients with CMA who reacted to methylprednisolone, skin prick test or intradermal test resulted positive only to methylprednisolone sodium succinate 40 mg but not to different methylprednisolone formulation that are free of lactose (11, 14). These reports have led to contraindicate the use of methylprednisolone injections containing lactose in patients with CMA or suspected to be allergic to cow's milk proteins (15). Allergic reactions to methylprednisolone injections containing lactose have been reported mainly in asthmatic children (15). However, physicians should always consider that clinical hypersensitivity reactions to corticosteroids can occur also when lactose-free preparations are given (16). Therefore, in selected cases drug provocation challenge may be required to reach a firm diagnosis (17).

Caseins have been found by ELISA at low concentration (8.1 and 18.3 ng/mL) in culture media of DTP (18). Along this line, it has been reported that 6 out of 8 children with anaphylaxis after receiving DTP injection have had immediate allergic reactions to milk proteins (19). However, it is reassuring that the Vaccine Adverse Event Reporting System database does not record reactions caused by DTP in patients with CMA (18).

Oral route

Cow's milk protein can be detected in oral polio vaccine (OPV), probiotics and lactulose. OPV provoked immediate severe allergic reactions in 4 children with positive skin prick test result and positive serum IgE antibodies to milk. Children had also positive skin prick test to OPV. Alfa-lactalbumin was found in OPV by ELISA (20).

Adverse reactions to probiotics have been rarely reported (21, 22). Anaphylaxis to a probiotic compound has been described in an infant allergic to milk with acute gastroenteritis (23). Subsequently, in the probiotic preparation it has been detected beta-lactoglobulin binding IgE from patients with CMA (24). Another study showed that 10 out of 11 probiotics contained cow's milk proteins (25). Lactulose is synthetically prepared from lactose. It has been demonstrated by oral challenge that lactulose syrup elicited rhinoconjunctivitis and wheezing in a child with high-level CMA. Authors hypothesized that milk proteins might have contaminated the medication and induced the reaction (26). Overall, these case reports raise the question whether tablets or oral solutions containing lactose are safe in children with severe CMA.

Conclusions

Patients with CMA have been sparsely reported to develop allergic reactions following administration of pharmaceuticals that have been contaminated with milk proteins with unpredictable lot-to-lot variability. We feel that it is unnecessary to avoid the administration of products that might be potentially contaminated with milk proteins in children with anaphylactic reaction to milk with the exception of methylprednisolone injections containing lactose of bovine origin (15). However, the risk of developing severe reactions suggests caution when such children receive medications that may potentially contain milk allergens. For example, a 1-hour surveillance should be performed at the office following administration of OPV or DPT (18). Finally, it is desirable that manufacturers remove or measure residual allergen content in the medications. This is necessary to definitively prevent allergic hypersensitivity reactions in patients with CMA.

Conflict of interest: None to declare

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Received: 24 January 2019

Accepted: 1 February 2019

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