Posted on Authorea 19 Dec 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.163994215.52769651/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Drug-induced enterocolitis syndrome with paracetamol (acetaminophen) in a 12-month-old-old boy.

Brice PASCAL[1], Bertrand Evrard[2], Etienne Merlin[1], Carole Egron[2], Benjamin Bonnet[1], and Elodie michaud[3]

[1]Clermont Auvergne University
[2]CHU Clermont-Ferrand
[3]CHU Estaing

December 19, 2021

Drug-induced enterocolitis syndrome with paracetamol (acetaminophen) in a 12-month-old-old boy

B.Pascal[ab], B.Evrard[ac], E.Merlin[bc], C.Egron[b], B.Bonnet[ac], E.Michaud[b]

[a] Service d'immunologie, hôpital Gabriel Montpied, Clermont-ferrand, France

[b] Service de pédiatrie générale, hôpital Estaing, Clermont-ferrand, France

[c] Université Clermont Auvergne, Clermont ferrand, France

To the Editor,

Drug-induced enterocolitis syndrome (DIES) is a new clinical presentation similar to food protein-induced enterocolitis syndrome (FPIES). It was described for the first time in 2014 by Novembre et al.(1). More and more cases have been described since and clinical diagnostic criteria have recently been proposed. (2)

A 12-month-old boy was referred to our Pediatric Allergy Unit for a suspected drug hypersensitivity. At age 10 months, he was admitted to the pediatric emergency room for vomiting and fever, previously treated with two intake of intrarectal paracetamol (15 mg/kg every 6 hours), the last one 4 hours before admission. He had no previous history (and no allergic history). During the initial examination, we observed asthenia, paleness, no fever (after antipyretics) and tachycardia, followed by four episodes of mucus vomiting without diarrhea. An occlusive syndrome was suspected. Given the hemodynamic disorders, continued fluid resuscitation was performed. Blood tests showed an isolated hyperleukocytosis with neutrophils (11.08 G/L). Eosinophils (0.210 G/L), lymphoid cells (7.25 G/L), the ionogramm and CRP (4.9 mg/L) were normal. Blood gas revealed a compensated respiratory alkalosis (lactates 2.2 mmol/L, methemoglobinemia 1.3%). No tryptase or specific IgE test was performed. Abdominal ultrasound was normal. Microbiological workup was negative. The next day, he was still irritable with several night vomiting episodes. He was discharged with some clinical improvement (diagnosed viral disease).

By questioning the parents, they noticed that their child presented digestive disorders' events at home since birth, which coincided with the 5 times intake of Paracetamol, twice orally and then intrarectally. The symptoms appeared systematically from the first intake. In the child's medical history, we found no rhythmicity related to meals or other etiologies. His father has a well-known pollen and Penicillin allergies. By reviewing the emergency room observations (Figure 1), we noticed systematic digestive disorders approximately 3h to 6h after each paracetamol intake, explaining the moderate initial clinical improvement.

Posted on Authorea 19 Dec 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.163994215.52769651/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Four months later, skin prick tests (10 mg/mL) and intradermal tests (0.1 mg/mL) were negative. The drug oral challenge (Table 1) was positive: repeated vomiting, marked pallor, lethargy, and crying without cutaneous or respiratory symptoms 2 hours after the last paracetamol intake. Rehydration and corticosteroid therapy brought a complete clinical recovery. No mast cell degranulation was observed (normal tryptase levels: 6.6 µg/L to 6.2 µg/L 1 hour after reaction). There was no infectious context or other confounding factors on the day of the challenge test.

We inferred a drug-induced enterocolitis syndrome (DIES) caused by paracetamol, in the absence of other plausible causes. This child's reaction met the various major and minor criteria described (3), independently of the dosage form, formally implicating paracetamol (Table 2). Therefore, the assay of specific immunoglobulins and the performance of a basophils activation test were not performed.

Based on all these observations, we decided to propose an alternative treatment with ibuprofen, if the child had fever and eliminate cross allergy, confirmed by a negative challenge test. We will follow the child and perhaps propose another Paracetamol challenge test, in a few years, to assess possible cure of the syndrome. Since the provocation test, parents kept paracetamol excluded, the child no longer presented any digestive disorder. Prognosis of the DIES is actually unknown. Oral challenge seems to be indeed the only useful test to confirm or exclude DIES (3). In contrast, skin tests don't provide conclusive evidence to diagnose DIES, as for FPIES.

This is the first clinical presentation of DIES with paracetamol. Similar cases following antibiotic intakes (including amoxicillin) and only one for pantoprazole have been described, with similar clinical and biological manifestations (2). DIES is a clinical entity more frequent in a pediatric population, described with a minimum age of 2 years old, but adult cases are more and more reported in the literature. The patient is therefore younger than the cases described in the literature.

Currently, it is considered in the literature that DIES is a syndrome equivalent to FPIES but with allergens of a different nature, respectively drug versus food. FPIES is a non-IgE mediated gastrointestinal food allergy (prevalence 1%), symptoms depend on the frequency of food exposure. FPIES affects infants and young children, diagnosis is clinical, and there are no specific biomarkers. In the literature, there were two kinds of FPIES being described: chronic FPIES occurs when food consumption is regular, symptoms (chronic diarrhea, vomiting, weight loss..) resolve with a period of avoidance, and acute FPIES occurs with occasional consumption of food and can have severe symptoms which may lead to shockSimilarly, DIES present specific criteria of non-IgE-mediated hypersensitivity, based only on the presence of typical symptoms (Table 2). However, to date, acute or chronic forms have not yet been described.

Although its clinical manifestations can be severe and lead to hypovolemic shock, DIES pathophysiology is still not well understood. There is also no validated biomarker. According to Powell and al (4), neutrophilia has been recognized as a common finding in patients presenting with acute FPIES for a long time. The increase of the eosinophil cationic protein (ECP) in stool samples from 24 and 48 h after the reaction was also described. (5) Many cases of FPIES will be probably described in the coming years, maybe with new different drugs. This diagnosis should be considered in the event of a recurrent digestive disorder, at any age.

To date, several unanswered questions need to be addressed. Clinicians must be known for example if DIES is a transient or persistent trouble. Further studies may allow to find the origin, evolution and treatment of DIES.

In conclusion, we reported the first DIES induced by PARACETAMOL, with tolerance to IBUPROFEN, confirmed by oral challenge test. Until now, it is the youngest patient case report and the first for PARACETAMOL.

Keywords: children; drug hypersensitivity reactions; drug-induced enterocolitis syndrome; drug allergy; antipyretic

References

Posted on Authorea 19 Dec 2021 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.163994215.52769651/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

1. Drug-Induced Enterocolitis Syndrome (DIES) Elio Novembre, Francesca Mori, Simona Barni, Neri Pucci,

2. Mori F, Liccioli G, Fuchs O et al. Drug-induced enterocolitis syndrome: Similarities and differences compared with food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol. 2021 Mar 2.

3. Van Thuijl AOJ, Landzaat LJ, Liem O, et al. Drug-induced enterocolitis syndrome (DIES): A clinical entity that deserves more awareness. Ann Allergy Asthma Immunol. 2019 May;122(5):538-539.

4. G K Powell. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance J Pediatr. 1976 May;88(5):840-4.

5. Freundt Serpa NP, Sánchez-Morillas L, Jaqueti Moreno P, González-Gutiérrez ML, Cimarra M, Cerecedo I, Fernández-Rivas M. Drug-Induced Enterocolitis Syndrome Due to Amoxicillin-Clavulanic Acid With Good Tolerance to Penicillin. J Investig Allergol Clin Immunol. 2020;30(4):301-302. doi: 10.18176/jiaci.0500. Epub 2020 Feb 25. PMID: 32101171.

Hosted file

`Figure 1.docx` available at https://authorea.com/users/451810/articles/550008-drug-induced-enterocolitis-syndrome-with-paracetamol-acetaminophen-in-a-12-month-old-old-boy

Hosted file

`Table 1.docx` available at https://authorea.com/users/451810/articles/550008-drug-induced-enterocolitis-syndrome-with-paracetamol-acetaminophen-in-a-12-month-old-old-boy

Hosted file

`Table 2.docx` available at https://authorea.com/users/451810/articles/550008-drug-induced-enterocolitis-syndrome-with-paracetamol-acetaminophen-in-a-12-month-old-old-boy