Drug-induced enterocolitis syndrome with acetaminophen in an adult: a call for diagnostic tools and accurate management

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Drug-induced enterocolitis syndrome (DIES) is an uncommon and poorly documented severe hypersensitivity non-IgE mediated reaction induced by drugs and characterized by gastrointestinal symptoms. Even though it’s potential severity, awareness of DIES is low and diagnostic tools and pathomechanisms involved are unexplored [1]. To the best of our knowledge, this is the first case report of DIES due to acetaminophen in an adult, confirmed with a positive lymphocyte transformation test (LTT).

We report the case of a 45-year-old man with no previous allergy history, develops repetitive vomiting and diarrhea 2-3 hour after the intake of argidol® 650 mg, (acetaminophen and codeine) taken as an antipyretic for an upper respiratory tract infection. Reports complete recovery in 24 hours. No medical attention was requested. Later tolerance to celecoxib was referred by the patient, but tolerance to other traditional non-steroidal anti-inflammatory drugs (NSAIDs) was unknown.

We performed skin prick tests with acetaminophen (10 mg/ml) and intradermal tests (0.1 mg/ml) with a negative result. Drug Provocation Test (DPT) was carried out with acetaminophen until a cumulative dose of 1 gram, presenting 2-3 hours after the last acetaminophen dose intake (being at home): pallor, abdominal discomfort, nausea and diarrhea with no other symptoms (neither cutaneous nor respiratory), resolved spontaneously in 24 hours. The study was catalogued as not conclusive and an underlying infectious gastrointestinal context was suspected. DPT was repeated one month later presenting, 2 hours after the final acetaminophen intake, more severe symptoms including: repetitive vomiting, abdominal pain, diarrhea, marked pallor, hypotension and dizziness. Once more the patient did not present skin or respiratory symptoms. Initially treated with oral corticoids (deflazacort® 60 mg) and antihistamine (bilaxten® 20 mg) with no improvement. Intravenous rehydration with saline 500 ml was prescribed with complete clinical recovery one hour after symptoms onset.

Based on the results of the oral challenge we suggest that our patient meets the criteria for DIES to acetaminophen as the patient meets the mayor criteria: vomiting in the 1- to 4-h period after ingestion of the suspected drug and absence of classic IgE-mediated allergic skin or respiratory symptoms; together with more than 3 minor criteria: a second episode
of repetitive vomiting after ingestion of the same drug, marked pallor, need for intravenous fluid support, diarrhea in 24 hours after ingested drug and hypotension. Additionally to the diagnostic criteria for patients presenting possible DIES, LTT was requested and carried out in Hospital Universitario La Paz with a positive result. Briefly, peripheral blood mononuclear cells (2×10^5 cells in 200 μL) were stimulated with 1, 10, 100 and 200 μg/mL of acetaminophen in triplicate for 6 days. For the final 18 hours of the incubation period, proliferation was determined by the addition of [3H] thymidine (0.5 μCi/well). Proliferative responses were calculated as stimulation index (SI), defined as the ratio between the mean values of counts per minute in cultures with drug and those obtained without drug. The LTT result was considered positive if the SI was higher than 2. The SI was 2.4 for 200 mg/mL acetaminophen (Supplementary figure).

In order to rule out potential cross-reactivity with other NASIDs, DPT was carried out with aspirin with good tolerance. Skin test and DPT with codeine resulted negative. Recommendation of avoidance of acetaminophen and paraminofenol family was given to the patient. Other NSAIDs were allowed along with codeine.

DIES to acetaminophen has been previously reported by Pascal et al in a 12-month-old child confirmed by oral challenge test [2]. First publication on the topic date in 2014 and up to date, other 11 clinical cases of DIES have been described in the literature: 8 children and 3 adults. Reported drugs were: amoxicillin or amoxicillin/clavulanate in 10 cases and pantoprazole in the remaining case [3-5].

Clinical presentation of DIES resembling food protein-induced enterocolitis syndrome (FPIES) seems clear, specific criteria have been proposed for diagnosis and potential existence of atypical forms have been described [6,7]. It has also been postulated that FPIES and DIES may also share common pathogenetic aspects as they are both non-immediate hypersensitivity reactions involving adaptive immunity [8]. However, pathogenesis of DIES remains unclear, the underlying immunologic mechanisms are still not verified, biomarkers not validated and predisposing genetic factors not known. Recently Mori et al, documented involvement of T cell in the pathogenesis of drug-induced enterocolitis syndrome reporting the first case of DIES with amoxicillin/clavulanate with a positive LTT, suggesting T-cell-mediated response in this entity [9]. In this sense, we propose LLT as a potentially useful and complementary tool for diagnosis of DIES when clinical criteria is met and suspicion is strong, due to the high risk and potential severity that involves DPT.

In the treatment of DIES, epinephrine has shown no effectiveness. It has been reported good response to antiemetics, intravenous rehydration and corticosteroids [1,2]. Our patient did not respond to antihistamines nether to corticosteroids but showed good response to intravenous fluids.
Because of the small number of cases identified, it is difficult to establish and rule whether DIES is a transient or persistent condition. The few cases reported suggest it is more frequent in children, but there is no available data concerning prognosis or natural history of DIES [6].

In conclusion, we present the first case of DIES due to acetaminophen described in an adult confirmed by oral challenge and a positive LTT. Potential cross-reactivity with other NSAIDs was ruled out. Informed consent to publication was obtained from the patient. We highlight the need for a better understanding of the pathomechanisms, natural history and prevalence of this particular disorder. We propose this case report as a call for clinicians to recognize DIES as a potentially severe hypersensitivity non IgE mediated reaction with a specific treatment. Further studies are needed to set up the correct management of these patients.

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**Conflict of interest:**

Any author has any conflict of interest.

**References**


