# Drug-Induced Enterocolitis Syndrome due to Acetaminophen in an Adult: A Call for Diagnostic Tools and Accurate Management

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J Investig Allergol Clin Immunol 2024; Vol. 34(4): 266-267
doi: 10.18176/jiaci.0970

Key words: Acetaminophen. Drug-induced enterocolitis syndrome. Pathogenesis. Lymphocyte transformation test. Adult.

Palabras clave: Paracetamol. Enterocolitis inducida por drogas. Patogénesis. Test de activación linfocitaria. Adulto.

Drug-induced enterocolitis syndrome (DIES) is an uncommon and poorly documented severe non–IgE-mediated hypersensitivity reaction caused by drugs and characterized by gastrointestinal symptoms. Even though DIES is a potentially severe condition, awareness is low and diagnostic tools and the pathogenic mechanisms involved are unexplored [1]. To our knowledge, this is the first report of a case of DIES due to acetaminophen in an adult that was confirmed with a positive lymphocyte transformation test (LTT) result. The patient gave his informed consent for the publication of this case report.

We report the case of a 45-year-old man with no previous allergy history who developed repetitive vomiting and diarrhea 2-3 hours after the intake of Argidol 650 mg (acetaminophen and codeine) as an antipyretic for an upper respiratory tract infection. The patient reported complete recovery in 24 hours. No medical care was requested. He also subsequently reported tolerance to celecoxib, although tolerance to other traditional nonsteroidal anti-inflammatory drugs (NSAIDs) was unknown.

We performed skin prick tests with acetaminophen (10 mg/mL) and intradermal tests (0.1 mg/mL), which yielded negative results. A drug provocation test (DPT) was carried out with acetaminophen until a cumulative dose of 1 g was reached. Some 3 hours after the last dose of acetaminophen (at home), the patient developed pallor, abdominal discomfort, nausea, and diarrhea, with no other symptoms (neither cutaneous nor respiratory). The symptoms resolved spontaneously in 24 hours. The study was considered inconclusive, and an underlying gastrointestinal infection was suspected. A DPT was repeated 1 month later. Two hours after the final dose of acetaminophen, the patient developed more severe symptoms including repetitive vomiting, abdominal pain, diarrhea, marked pallor, hypotension, and dizziness (again, without cutaneous or respiratory symptoms). He was treated initially with oral corticosteroids (deflazacort 60 mg) and an antihistamine (bilastine [Bilaxten] 20 mg), although his condition did not improve. Intravenous rehydration with saline 500 mL was prescribed, with complete recovery from symptoms 1 hour after onset.

Based on the results of the oral challenge, we considered that the patient met the major criteria for DIES due to acetaminophen (vomiting in the 1- to 4-hour period after ingestion 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 during the 24 hours after ingestion, and hypotension). In addition to the diagnostic criteria for patients presenting possible DIES, LTT was carried out in Hospital Universitario La Paz, Madrid and yielded a positive result. Briefly, peripheral blood mononuclear cells ($2\times10^5$ 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 the stimulation index (SI), defined as the ratio of mean values of counts per minute in culture with drug to those obtained without drug. The LTT result was considered positive if the SI was higher than 2. The SI was 2.4 for acetaminophen 200 mg/mL (Supplementary figure).

In order to rule out potential cross-reactivity with other NSAIDs, DPT was carried out with aspirin and showed good tolerance. Skin tests and DPT with codeine yielded negative results. The patient was recommended to avoid acetaminophen and other members of the para-aminophenol family. Alternative NSAIDs were allowed, along with codeine.

DIES due to acetaminophen confirmed by oral challenge test was reported by Pascal et al [2] in a 12-month-old child. The first publication on the topic dates from 2014; since then, a further 11 clinical cases of DIES have been reported (8 children and 3 adults). The drugs involved were amoxicillin or amoxicillin/clavulanate in 10 cases and pantoprazole in the remaining case [3-5].

Clinically, DIES resembles food protein-induced enterocolitis syndrome (FPIES). Specific criteria have been proposed for diagnosis, and the potential existence of atypical forms has been described [6,7]. It has also been postulated that FPIES and DIES share common pathogenic mechanisms, as they are both nonimmediate hypersensitivity reactions involving adaptive immunity [8]. However, the pathogenesis

 

of DIES remains unclear, the underlying immunologic mechanisms have not been verified, biomarkers have not been validated, and predisposing genetic factors are not known. Mori et al [9] recently documented involvement of T cells in the pathogenesis of DIES, reporting the first case of DIES with amoxicillin/clavulanate and a positive LTT result, findings suggestive of a T cell–mediated response. Given the high risk and potential severity of DPT, we propose LLT as a potentially useful and complementary tool for diagnosis of DIES when the clinical criteria are met and the suspicion is strong.

Epinephrine is not effective for the treatment of DIES. Favorable responses have been reported with antiemetics, intravenous rehydration, and corticosteroids [1,2]. In the present case, the patient did not respond to antihistamines or to corticosteroids, although he did respond well to intravenous fluids.

Because of the small number of cases reported, it is difficult to establish whether DIES is a transient or persistent condition. The symptoms seem to be more frequent in children, although no data are available on prognosis or natural history [6].

In conclusion, we present the first case of DIES due to acetaminophen in an adult confirmed by oral challenge and a positive LTT result. Potential cross-reactivity with other NSAIDs was ruled out. We highlight the need for a better understanding of the pathogenic mechanisms, natural history, and prevalence of this disorder. We propose this case report as a call for clinicians to recognize DIES as a potentially severe non–IgE-mediated hypersensitivity reaction requiring specific treatment. Further studies are needed to establish appropriate management of affected patients.

*Funding*

The authors declare that no funding was received for the present study.

*Conflicts of Interest*

The authors declare that they have no conflicts of interest.

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*Manuscript received September 29, 2023; accepted for publication November 6, 2023.*

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