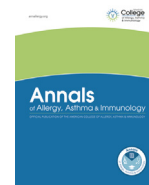




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Letter

When voluntary paracetamol overdose requires a drug challenge

Paracetamol (acetaminophen), an extremely widely used nonsteroidal anti-inflammatory (NSAID) and analgesic drug, is an over-the-counter medication in many countries.¹ It is also one of the most frequently used drugs, either alone or in combination, in cases of deliberate self-poisoning in adults and children.² Paracetamol overdoses are well known for their hepatotoxicity, leading to extensive hepatic destruction, particularly when combined with opioid.¹ Cardiotoxicity, metabolic acidosis, and electrolytes imbalance attributable to kidney damage have also been reported. Death, linked or not to hepatic failure, is possible, with paracetamol representing 2.6% of the deaths caused by fatal poisoning in England and Wales in 2011.³ Reductions in pack size, continued publicity about the dangers of paracetamol overdose, and improved liver failure treatment, such as transplantation, unfortunately do not result in a decreased number of fatalities.³ We describe an adolescent with angioedema and urticaria after the ingestion of paracetamol at very high doses, which raises questions about the necessity of performing a drug challenge in such a case.

A 14-year-old girl was hospitalized for the deliberate ingestion of 16 g of paracetamol. The patient, whose medical record included chronic depression, had previously received paracetamol and other NSAIDs (acetylsalicylic acid, ibuprofen), when needed, because of vertebral disk pinching with chronic lumbar pain, with no reported reaction. She had no history of atopy or acute or chronic urticaria. In the 2 hours after the suicide attempt, the patient developed facial edema and generalized urticaria, resulting in her transfer to a tertiary care hospital. Consciousness and hemodynamic evaluation were normal on arrival at the hospital. Treatment with oral cetirizine and intravenous *N*-acetylcysteine was initiated, and the patient was referred to our unit. Liver enzyme levels were in the reference range. Paracetamol blood level at admission was above the toxic zone (112 mg/L at 4 hours after the overdose), and *N*-acetylcysteine treatment was rapidly stopped thereafter. There were no other detectable toxic elements in the blood and urine. The patient was discharged and allowed to return home after 72 hours of hospitalization.

Following psychiatric evaluation and the agreement of the psychiatrists, we decided to explore 1 month later a possible IgE-mediated mechanism and to reintroduce paracetamol at a therapeutic dose. Skin prick tests were refused by the patient. Oral challenge with progressive increased doses every 30 minutes (10, 50, 100, 250, 500, and 1500 mg, cumulative dose of 2,410 mg) was well tolerated, and additional paracetamol intake when needed was authorized. A safe reintroduction of paracetamol, acetylsalicylic acid, and ibuprofen at usual doses took place 3 days, 20 days, and 3 months, respectively, after the paracetamol challenge.

Hypersensitivity reactions to paracetamol are extremely rare when given at usual therapeutic doses. In adults, most of these reactions occur in patients with a NSAID-induced urticaria or angioedema but sometimes may result from a hypersensitivity reaction to paracetamol only (single NSAID-induced urticaria, angioedema, or anaphylaxis).⁴ In France, paracetamol has been incriminated in 3% of the cases of anaphylaxis.⁵ In children, NSAIDs are the second cause of hypersensitivity reactions and the main observed clinical manifestations in 80% of cases are urticaria and/or angioedema cases, with no generalized reaction, especially in cases mediated by a nonimmunological mechanism.^{6,7} The diagnosis of paracetamol hypersensitivity reaction relies mainly on oral challenge tests.^{4,7} Indeed, skin prick tests have a low sensitivity, with only a limited number of selective responders to paracetamol having positive skin test results.^{4,6,7} Use of *in vitro* tests is controversial.^{4,6,7} Thus, oral challenge tests are the gold standard to ascertain paracetamol hypersensitivity.^{4,6,7} Challenge protocols are various, from a 2-step graduated oral challenge beginning with one-fourth or one-tenth of the dose followed by a standard therapeutic dose preferred in the United States to a multiple challenge steps recommended in Europe.^{4,6–9} Of note, 4% to 15.5% of the suspected cases of paracetamol hypersensitivity are confirmed by means of an oral challenge test.⁷

Our case report is unusual because the patient had previously received therapeutic doses of paracetamol, which had not induced any adverse reaction, but had experienced a prominent clinical reaction shortly after a massive intake of the drug. No other drug was absorbed concomitantly. Of note, urticaria and angioedema followed paracetamol absorption but preceded *N*-acetylcysteine administration, which is important because *N*-acetylcysteine itself may induce immediate reactions in up to 10% of patients.¹⁰ Despite the clinical presentation, the oral challenge results suggest that this patient has no IgE-mediated hypersensitivity to paracetamol. Because other NSAIDs have been used with no problem after the massive ingestion episode, a cross-reaction to NSAIDs appears unconvincing, even in the absence of an acetylsalicylic challenge. Thus, this case illustrates that ingestion of very high doses of paracetamol may mimic a pseudoallergic reaction to paracetamol, likely through cyclo-oxygenase 1 inhibition.⁴ In such a case, in which a toxic mechanism is finally suspected, a drug challenge is indicated despite the circumstances surrounding the incident. In our opinion, a collaboration between the allergist and the psychiatrist is required in such cases.

In conclusion, our case report underscores the importance of the oral challenge test in cases of suspected allergy to paracetamol, even in the case of massive voluntary absorption. It also confirms the dogma of the toxicology father (Paracelse, 1493–1541): “All the things are poison, and nothing is without poison; solely the dose determines that a thing is not a poison.”

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References

- [1] Graham GG, Davies MJ, Day RO, et al. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*. 2013;21:201–232.
- [2] Hedeland RL, Jorgensen MH, Teilmann G, et al. Childhood suicide attempts with acetaminophen in Denmark: characteristics, social behavior, trends and risk factors. *Scand J Public Health*. 2013;41:240–246.
- [3] Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000–2011. *Clin Toxicol (Phila)*. 2014;52:1–12.
- [4] Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68:1219–1232.
- [5] Renaudin JM, Beaudouin E, Ponvert C, et al. Severe drug-induced anaphylaxis: analysis of 333 cases recorded by the Allergy Vigilance Network from 2002 to 2010. *Allergy*. 2013;68:929–937.
- [6] Blanca-Lopez N, Cornejo-Garcia JA, Pérez-Alzate D, et al. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in children and adolescents: selective reactions. *J Investig Allergol Clin Immunol*. 2015;25:385–395.
- [7] Ortega N, Dona I, Audicana MT, et al. Practical guidelines for diagnosing hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *J Investig Allergol Clin Immunol*. 2014;24:308–323.
- [8] Solensky R, Khan D; Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.
- [9] Iammatteo M, Blumenthal KG, Saff R, et al. Safety and outcomes of test doses for the evaluation of adverse drug reactions: a 5-year retrospective review. *J Allergy Clin Immunol Pract*. 2014;2:768–774.
- [10] Yamamoto T, Spencer T, Dargan PI, et al. Incidence and management of N-acetylcysteine-related anaphylactoid reactions during the management of acute paracetamol overdose. *Eur J Emerg Med*. 2014;21:57–60.