ORIGINAL RESEARCH PAPER

Immunology

KEY WORDS: Paracetamol; Acetaminophen; Dolo 650; Immediate Drug Hypersensitivity; Drug Provocation Test; Naproxen; Urticaria; Ulcerative Colitis.

SELECTIVE IMMEDIATE HYPERSENSITIVITY TO PARACETAMOL (ACETAMINOPHEN) CONFIRMED BY ORAL DRUG PROVOCATION TESTING WITH DOLO 650 AND DEMONSTRATED NAPROXEN TOLERANCE IN A PATIENT WITH ULCERATIVE COLITIS: A CASE REPORT

Dr Hitesh Billa Lakshmi* Consultant Allergy Specialist and Interventional Pulmonologist, Assistant Professor, Department of Respiratory Medicine Apollo Institute of Medical Sciences and Research (AIMSR), Apollo Health City, Hyderabad, Telangana, India. *Corresponding Author

Dr Sowjanya Patibandla Regional Clinical Director and Senior Consultant, Emergency Medicine Apollo Hospitals, Jubilee Hills, Hyderabad, Telangana, India.

Dr Srikar Darisetty Senior Consultant, Interventional Pulmonology and Sleep Medicine Apollo Hospitals, Jubilee Hills, Hyderabad, Telangana, India.

Dr Krishna Priya Meegada Postgraduate Resident, Department of Respiratory Medicine Apollo Institute of Medical Sciences and Research (AIMSR), Apollo Health City, Hyderabad, Telangana, India.

Dr Nithya Reddy Kalluri Postgraduate Resident, Department of Respiratory Medicine Apollo Institute of Medical Sciences and Research (AIMSR), Apollo Health City, Hyderabad, Telangana, India.

Dr Indhu Mallipeddi Postgraduate Resident, Department of Respiratory Medicine Apollo Institute of Medical Sciences and Research (AIMSR), Apollo Health City, Hyderabad, Telangana, India.

ABSTRACT

Background: Paracetamol (acetaminophen) is widely used as an analgesic and antipyretic, particularly in patients for whom conventional nonsteroidal anti-inflammatory drugs (NSAIDs) may be undesirable. Although generally well tolerated, paracetamol can cause immediate hypersensitivity reactions. Differentiating selective paracetamol hypersensitivity from cross-reactive NSAID intolerance is important for diagnostic accuracy and identification of suitable therapeutic alternatives. **Case Presentation:** We report a male patient with ulcerative colitis who experienced two episodes of urticaria approximately one hour after paracetamol exposure. The first episode followed oral Dolo 650 (paracetamol 650 mg) during bowel preparation for colonoscopy and was complicated by hypotension documented before drug administration and subsequent postural blackout episodes. The second episode occurred following intravenous paracetamol administered after a sports-related injury; the brand and complete formulation details were unavailable. This reaction was limited to cutaneous manifestations without documented systemic involvement. A supervised graded oral drug provocation test (DPT) using Dolo 650 was subsequently performed. The patient tolerated an initial 65 mg dose but developed objective urticaria, pruritus and erythema following an additional 130 mg, at a cumulative administered dose of 195 mg. The challenge was discontinued and classified as positive. A subsequent supervised graded oral naproxen challenge reached a cumulative dose of 650 mg without documented immediate hypersensitivity manifestations. **Discussion:** The positive oral DPT established clinical hypersensitivity to the tested Dolo 650 preparation. The historical reactions and contrasting naproxen tolerance supported a selective immediate paracetamol hypersensitivity phenotype rather than generalized cross-reactive COX-1-mediated NSAID intolerance. However, the immunological mechanism was not established, and a formulation-specific contribution could not be completely excluded. The naproxen challenge employed shorter-than-recommended inter-dose intervals, limiting the certainty of its negative interpretation. **Conclusion:** This case highlights the importance of detailed clinical chronology, individualized risk assessment and supervised DPT in evaluating suspected paracetamol hypersensitivity. It also emphasizes the need to distinguish immediate allergy tolerance from the gastrointestinal suitability of alternative analgesics in patients with ulcerative colitis.

INTRODUCTION

Paracetamol, also known as acetaminophen, is among the most commonly used analgesic and antipyretic medications worldwide. Although generally well tolerated, immediate hypersensitivity reactions have been reported, ranging from isolated urticaria and angioedema to severe systemic manifestations. Diagnostic evaluation may be challenging because suspected reactions frequently occur in the presence of concurrent medications, underlying illnesses and physiological cofactors. The European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy (EAACI/ENDA) position paper emphasizes the importance of detailed clinical assessment, individualized risk stratification and appropriately supervised drug provocation testing (DPT) in selected patients [1].

Hypersensitivity reactions to NSAIDs and related analgesics are broadly divided into cross-reactive and selective phenotypes. Cross-reactive reactions are generally associated with cyclooxygenase-1 (COX-1) inhibition and may occur following exposure to multiple chemically unrelated NSAIDs. In contrast, selective reactions involve an individual medication or a limited group of related drugs, while tolerance to other analgesics may be preserved. The updated diagnostic algorithm for NSAID hypersensitivity and the World Allergy Organization (WAO) statement emphasize the importance of distinguishing these phenotypes through clinical history and appropriately selected diagnostic procedures [2,3].

The contemporary classification framework builds on earlier EAACI/ENDA recommendations distinguishing NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease, NSAID-induced urticaria/angioedema

and selective immediate reactions [4]. Pediatric EAACI/ENDA recommendations similarly emphasize the importance of distinguishing selective reactions from cross-reactive NSAID hypersensitivity, although their clinical application must be adapted to the population being evaluated [5]. Structured diagnostic algorithms have further highlighted the role of culprit-drug evaluation and alternative-drug provocation in establishing clinically useful treatment options [6].

Paracetamol differs pharmacologically from conventional NSAIDs because of its relatively weak peripheral COX-1 inhibitory activity. Nevertheless, it may trigger reactions in patients with cross-reactive NSAID hypersensitivity and can also produce selective immediate hypersensitivity. Rutkowski and colleagues investigated patients with suspected paracetamol allergy and demonstrated that confirmed paracetamol hypersensitivity may coexist with tolerance to other NSAIDs, while the underlying immunological mechanisms remain heterogeneous [7].

Clinical history remains essential for identifying suspected analgesic hypersensitivity, although it may not reliably distinguish selective from cross-reactive reactions in every patient. Studies examining the diagnostic value of clinical history have highlighted the importance of reaction timing, the number of implicated drugs and objective confirmation through provocation testing when clinically appropriate [8].

The diagnostic and therapeutic implications become particularly important in patients with ulcerative colitis, for whom conventional NSAIDs may be undesirable because of gastrointestinal toxicity and concerns regarding inflammatory bowel disease exacerbation. Consequently, paracetamol may represent an important option for fever and pain management. We report a patient with ulcerative colitis who developed recurrent urticaria following exposure to oral Dolo 650 and an unidentified injectable paracetamol formulation, subsequently confirmed by positive oral DPT using Dolo 650, with demonstrated immediate tolerance to naproxen during a supervised alternative-drug challenge.

Case Presentation

A male patient with a known history of ulcerative colitis receiving medical management was referred for evaluation of suspected paracetamol hypersensitivity. He was not routinely taking antihistamines or systemic corticosteroids and had no previously documented history of anaphylaxis or known paracetamol hypersensitivity before the first described episode. Paracetamol was considered clinically useful for fever and analgesia because conventional NSAID use was generally undesirable in the context of his underlying inflammatory bowel disease.

The first suspected reaction occurred while the patient was undergoing bowel preparation for colonoscopy. He was fasting and experienced loose stools that disrupted his normal daily activities. Importantly, hypotension was documented before paracetamol administration. He subsequently received oral Dolo 650, containing paracetamol 650 mg, in temporal proximity to mesalamine. Approximately one hour after medication administration, he developed urticaria, which showed mild improvement following antihistamine treatment.

While travelling to the emergency department, the patient experienced a transient blackout episode while standing. His symptoms improved after lying down without additional intervention. He subsequently received pheniramine and hydrocortisone, following which his symptoms improved. Epinephrine was not administered. Approximately three hours later, he experienced another blackout episode while standing, accompanied by involuntary passage of stool and hypotension. His condition improved following intravenous fluid administration, and he was discharged the following day.

The first episode raised suspicion of immediate hypersensitivity to Dolo 650. However, the accompanying cardiovascular manifestations required cautious interpretation because hypotension had already developed before drug exposure. Fasting, bowel preparation, loose stools, possible volume depletion and concurrent mesalamine administration represented potential confounding factors. Although the subsequent blackout episodes occurred after medication administration, their postural nature and improvement with recumbency or intravenous fluids suggested a possible non-allergic circulatory contribution. The available information was insufficient to definitively attribute or exclude these later events as paracetamol-related systemic hypersensitivity.

The second episode occurred following a football-related injury. The patient received bilastine approximately two minutes before intravenous paracetamol administration. Approximately 60% of the intended intravenous paracetamol dose had been administered. The brand name, manufacturer and complete excipient composition of the injectable preparation were unavailable. About one hour after exposure, he developed cutaneous manifestations consistent with urticaria. There was no documented hypotension, fall in blood pressure, respiratory compromise or other systemic involvement. Symptoms improved following antihistamine treatment.

The recurrence of similar cutaneous manifestations following exposure to oral Dolo 650 and an injectable paracetamol formulation strengthened suspicion of immediate paracetamol hypersensitivity. Nevertheless, the historical episodes occurred in the presence of potential cofactors, and the exact formulation of the injectable preparation was unknown. Therefore, a molecule-specific immunological mechanism could not be established from the historical information alone. A structured specialist assessment was undertaken to clarify the diagnosis and determine whether paracetamol could remain a therapeutic option.

Diagnostic Assessment and Clinical Reasoning

The diagnostic evaluation focused on determining whether the recurrent cutaneous manifestations were causally associated with paracetamol exposure, whether the historical cardiovascular events represented drug-induced anaphylaxis and whether an alternative analgesic could be identified.

The history was compatible with an immediate hypersensitivity phenotype because urticaria developed approximately one hour after paracetamol exposure on two occasions. However, the first episode was complicated by hypotension preceding medication administration and subsequent postural blackout episodes, whereas the second reaction was limited to cutaneous symptoms. Therefore, the available clinical history was considered suggestive of paracetamol hypersensitivity but insufficient to establish paracetamol-induced anaphylaxis.

The decision to perform supervised DPT was influenced by the clinical importance of paracetamol in a patient with ulcerative colitis, uncertainty regarding the historical reactions and the need for objective diagnostic clarification. EAACI/ENDA recommendations emphasize that DPT should be undertaken only after individualized assessment of the expected diagnostic benefit and potential risks, with consideration of previous reaction severity, comorbidities, available alternatives and the capacity to recognize and manage severe reactions [1].

An IgE-mediated mechanism was considered possible but could not be established from the history. Skin testing and in vitro investigations for paracetamol have limited validation,

and negative results would not reliably exclude hypersensitivity. Supervised oral DPT using Dolo 650 was therefore selected following specialist clinical assessment. The absence of confirmed historical anaphylaxis was not considered equivalent to an absence of risk.

Paracetamol Drug Provocation Test

A supervised graded oral DPT using Dolo 650 (paracetamol/acetaminophen) was performed on October 3, 2026. The planned challenge involved incremental oral doses toward a cumulative therapeutic target of 650 mg. The patient was clinically stable at baseline. An initial dose equivalent to 65 mg of paracetamol was administered and tolerated without symptoms. A subsequent dose equivalent to 130 mg was then administered, resulting in a cumulative dose of 195 mg.

Following the second dose, the patient developed objective wheals behind the ears, associated pruritus and erythema. No respiratory, cardiovascular, gastrointestinal or other systemic involvement was documented during the observed reaction. The challenge was immediately discontinued, and no further paracetamol was administered. The planned therapeutic target of 650 mg was therefore not reached.

Table 1. Graded Oral Drug Provocation Test Using Dolo 650

Step	Administered paracetamol dose	Cumulative dose	Clinical response
Baseline	—	—	Clinically stable
1	65 mg	65 mg	Tolerated
2	130 mg	195 mg	Urticaria, pruritus and erythema
Further doses	Not administered	—	Challenge discontinued

The development of objective urticaria following supervised oral Dolo 650 exposure was interpreted as a positive DPT, confirming clinically relevant immediate hypersensitivity to the tested preparation under the challenge conditions. The observed reaction reproduced the predominant cutaneous phenotype described during the historical episodes. However, the positive challenge did not independently establish an IgE-mediated mechanism, and the isolated cutaneous reaction did not meet documented criteria for anaphylaxis.



The initial 65 mg dose represented one-tenth of the planned 650 mg therapeutic target, consistent with a reduced starting-dose approach in selected patients. Nevertheless, the appropriateness of the complete protocol depends on individualized risk assessment, including the historical episodes of hypotension and transient loss of consciousness. The challenge was discontinued following development of objective urticaria, consistent with the principle of avoiding unnecessary continued exposure once a clinically meaningful positive endpoint has been reached [1].

Although the positive DPT confirmed hypersensitivity to the tested Dolo 650 preparation, the possibility of a formulation-specific contribution could not be completely excluded. However, the history of a similar cutaneous reaction following an injectable paracetamol preparation supported paracetamol as the likely common culprit. Because the injectable formulation details were unavailable, the findings should not be presented as definitive mechanistic proof of hypersensitivity to the active molecule independently of excipients.

Naproxen Drug Provocation Test

Following confirmation of hypersensitivity to Dolo 650, a supervised oral naproxen DPT was undertaken to evaluate a potentially tolerated alternative analgesic. Naproxen was selected because it is a conventional NSAID with strong COX-1 inhibitory activity. Demonstration of tolerance to naproxen would provide additional evidence relevant to distinguishing selective paracetamol hypersensitivity from generalized cross-reactive NSAID intolerance [2–4].

The naproxen DPT was performed on October 14, 2026, beginning at approximately 11:00 AM. The reported preparation concentration was 50 mg/mL. Sequential oral doses of 50 mg, 100 mg, 150 mg, 200 mg and an additional 150 mg were administered, corresponding to cumulative doses of 50 mg, 150 mg, 300 mg, 500 mg and 650 mg, respectively. The total administered volume was 13 mL, and the reported intervals between incremental doses were approximately 15–20 minutes.

Table 2. Graded Oral Naproxen Drug Provocation Test

Step	Volume	Dose	Cumulative dose	Response
1	1 mL	50 mg	50 mg	Tolerated
2	2 mL	100 mg	150 mg	Tolerated
3	3 mL	150 mg	300 mg	Tolerated
4	4 mL	200 mg	500 mg	Tolerated
5	3 mL	150 mg	650 mg	Tolerated

The patient tolerated all administered doses without documented immediate urticaria, angioedema, bronchospasm, respiratory compromise, hypotension or anaphylaxis during the recorded observation period. The challenge was classified as negative for immediate hypersensitivity at a cumulative administered dose of 650 mg.

This result demonstrated observed immediate tolerance to naproxen under the conditions of testing. However, the documented 15–20-minute inter-dose intervals were shorter than the intervals recommended in the EAACI/ENDA DPT position paper. The exact duration of observation following the final dose was not available in the supplied records. These limitations reduce the certainty with which later-developing reactions can be excluded and must be acknowledged when interpreting the negative result [1].

Despite these limitations, the contrasting responses to Dolo 650 and naproxen provided clinically relevant evidence supporting a selective immediate paracetamol hypersensitivity phenotype. The negative naproxen challenge did not establish tolerance to other NSAIDs, exclude delayed reactions or guarantee tolerance during future therapeutic exposures.

DISCUSSION

Selective Paracetamol Hypersensitivity and Contemporary Classification

The principal diagnostic observation in this case was the contrasting response to Dolo 650 and naproxen during supervised oral provocation testing. The patient developed objective urticaria following a cumulative paracetamol dose of 195 mg administered as Dolo 650 but tolerated a cumulative naproxen dose of 650 mg without a documented immediate hypersensitivity reaction. This pattern favors selective immediate paracetamol hypersensitivity rather than generalized cross-reactive COX-1-mediated intolerance.

The contemporary classification of NSAID hypersensitivity

distinguishes cross-reactive reactions from selective immediate and delayed phenotypes. Cross-reactive reactions are generally associated with COX-1 inhibition and may involve multiple chemically unrelated NSAIDs. Selective immediate reactions, in contrast, may occur following exposure to one drug or a limited group of related drugs, with tolerance to other NSAIDs preserved [2–4].

The selective immediate phenotype known as single-NSAID-induced urticaria, angioedema or anaphylaxis (SNIUAA) provides a useful conceptual framework for interpreting isolated analgesic reactions. However, paracetamol is pharmacologically distinct from conventional NSAIDs, and the available findings do not establish a specific immunological pathway. Therefore, the most defensible diagnostic description is clinically confirmed immediate hypersensitivity to Dolo 650, with a selective paracetamol hypersensitivity phenotype supported by naproxen tolerance.

The findings are consistent with observations by Rutkowski and colleagues, who investigated 32 patients with suspected paracetamol allergy. Paracetamol hypersensitivity was confirmed in 16 patients, of whom 12 (75%) tolerated NSAIDs based on challenge testing or clinical history. The authors also demonstrated that a specific IgE mechanism may be present in a subset of patients, while negative skin testing does not exclude paracetamol hypersensitivity [7].

The present case similarly demonstrates clinically confirmed hypersensitivity to a paracetamol-containing product with observed tolerance to a conventional strong COX-1 inhibitor. However, the mechanism remains undetermined, and tolerance to naproxen alone does not establish unrestricted tolerance to other NSAIDs.

Clinical Chronology and Interpretation of Suspected Anaphylaxis

A particularly instructive feature of this case was the occurrence of hypotension and transient blackout episodes during the first historical reaction. The chronology was important because hypotension had been documented before Dolo 650 administration. Subsequently, the patient experienced postural blackout episodes, with improvement after recumbency or intravenous fluid administration.

These findings raised the possibility of orthostatic or volume-related circulatory compromise in the setting of fasting, bowel preparation and loose stools. However, the precise cause of the blackout episodes was not established, and their occurrence after medication administration means that an allergic contribution cannot be conclusively excluded retrospectively.

Studies of NSAID hypersensitivity have demonstrated that reactions may involve multiple organ systems, including blended clinical patterns with cutaneous, respiratory and gastrointestinal manifestations. Consequently, classification requires evaluation of the complete clinical phenotype rather than reliance on isolated symptoms [9].

Contemporary anaphylaxis practice parameters emphasize the importance of clinical presentation, organ involvement, exposure chronology and appropriate interpretation of cardiovascular manifestations. Hypotension or collapse may be important features of anaphylaxis, but their attribution to a specific medication requires a compatible temporal and clinical relationship [10,11].

In the present case, the second historical reaction and the supervised Dolo 650 DPT were associated with cutaneous manifestations without documented respiratory or cardiovascular compromise. Therefore, the available evidence established immediate hypersensitivity to the tested paracetamol-containing preparation but did not confirm paracetamol-induced anaphylaxis. Importantly, this conclusion does not exclude the possibility of a more severe reaction during future exposure.

Role of Drug Provocation Testing

Drug provocation testing is an important component of contemporary drug allergy evaluation when individualized clinical risk assessment supports its use. The EAACI/ENDA position paper identifies DPT as the diagnostic reference standard and emphasizes careful patient selection, appropriate dosing, monitoring, observation and recognition of positive stopping criteria [1].

In the present case, the Dolo 650 DPT reproduced objective urticaria during controlled oral exposure. The reaction occurred at a cumulative dose below the planned therapeutic target, establishing clinical hypersensitivity to the tested product without the need for further administration. The positive challenge strengthened causal attribution to Dolo 650 despite the presence of potential cofactors during the historical episodes.

Alternative-drug challenges serve a complementary clinical purpose by identifying medications that may be tolerated. The practical value of structured NSAID provocation testing has been demonstrated in clinical studies, including the retrospective study by Li and colleagues evaluating two-step outpatient NSAID challenges [12].

The naproxen challenge in this patient provided evidence of observed immediate tolerance, but the shorter-than-recommended dosing intervals and incompletely documented post-final-dose observation were important limitations. Accordingly, the negative result should be interpreted according to the actual protocol rather than presented as equivalent to a fully documented guideline-concordant challenge.

Immunological Mechanisms and Diagnostic Limitations

The mechanism underlying selective immediate paracetamol hypersensitivity remains incompletely characterized. Although some selective immediate reactions may involve drug-specific immunological mechanisms, the presence of urticaria and a positive DPT does not independently demonstrate IgE mediation.

Paracetamol hypersensitivity studies have explored the potential role of specific IgE, but the diagnostic performance of skin testing and available in vitro investigations remains limited [7]. The basophil activation test has emerged as a potentially useful complementary investigation for selected immediate drug hypersensitivity reactions. However, the EAACI task force position paper emphasizes that diagnostic performance varies across drug classes and that standardization remains an important limitation [13].

In the present case, serum tryptase sampling was advised following the observed challenge reaction, but the results were not available in the supplied documentation. An increase in serum tryptase could support mast-cell activation but would not independently establish drug-specific IgE mediation. Conversely, normal tryptase concentrations would not exclude an isolated cutaneous hypersensitivity reaction.

The positive DPT established hypersensitivity to the tested Dolo 650 preparation. The history of a similar reaction following an injectable paracetamol formulation supported a common paracetamol-related trigger. However, because the injectable brand and excipient composition were unknown, a formulation-specific contribution could not be excluded. The most appropriate conclusion therefore remains clinically confirmed immediate hypersensitivity to Dolo 650, with a likely selective paracetamol hypersensitivity phenotype and

an undetermined immunological mechanism.

Clinical Importance of Ulcerative Colitis

The underlying ulcerative colitis was an important determinant of the diagnostic and therapeutic approach. Paracetamol is often a useful antipyretic and analgesic in patients with inflammatory bowel disease because conventional NSAIDs may be associated with gastrointestinal adverse effects and concerns regarding disease exacerbation.

The relationship between NSAID exposure and inflammatory bowel disease exacerbation is complex. Cohen-Mekelburg and colleagues investigated this association using multiple analytical approaches and demonstrated that residual confounding and reverse causality may influence the observed relationship between NSAID exposure and subsequent disease activity [14]. These findings suggest that NSAIDs should not automatically be considered universally contraindicated in all patients with inflammatory bowel disease, although individualized assessment remains necessary.

In the present case, confirmation of hypersensitivity to Dolo 650 created a practical therapeutic challenge because an otherwise useful medication could no longer be recommended for unsupervised use. The negative naproxen challenge identified a potentially tolerated alternative from an immediate allergy perspective but did not establish its gastrointestinal suitability.

Any future therapeutic use of naproxen should therefore involve assessment of ulcerative colitis activity, gastrointestinal bleeding risk, concomitant medications and treatment duration, ideally in consultation with the treating gastroenterologist. This case illustrates that immunological tolerance demonstrated during DPT does not necessarily establish the overall clinical appropriateness of a medication.

Management and Patient Counselling

Following the positive Dolo 650 DPT, the patient was advised to avoid Dolo 650 and other paracetamol-containing medications, including combination cold, flu and analgesic preparations, pending specialist reassessment. Documentation of the confirmed hypersensitivity in the medical record was recommended, including the tested brand, observed reaction phenotype and positive challenge result.

An adrenaline auto-injector was prescribed as an individualized precaution, together with counselling regarding recognition of anaphylaxis and appropriate emergency management. The patient was advised that isolated uncomplicated urticaria does not routinely require epinephrine, whereas suspected anaphylaxis warrants prompt intramuscular epinephrine and urgent medical assessment. This approach is consistent with contemporary anaphylaxis management recommendations emphasizing epinephrine as first-line treatment for anaphylaxis [10,11].

Following the negative naproxen DPT, the patient was informed that immediate tolerance had been demonstrated under supervised conditions. However, unsupervised NSAID use remained discouraged because of the underlying ulcerative colitis. Gastroenterology assessment was recommended before considering naproxen for future therapeutic use.

The patient was advised to report delayed cutaneous manifestations and attend follow-up for review of the challenge outcomes, any available tryptase results and individualized analgesic planning. Actual longer-term follow-up outcomes require confirmation from the clinical records.

Strengths and Limitations

The principal strength of this case was objective confirmation of hypersensitivity to Dolo 650 following two historical episodes involving oral and intravenous paracetamol exposures. The supervised oral challenge reproduced the predominant cutaneous manifestations and strengthened causal attribution to the tested preparation. The subsequent naproxen challenge provided additional evidence supporting a selective hypersensitivity phenotype. Furthermore, the case demonstrates the importance of accurate chronology when systemic manifestations occur in the presence of physiological stress and potential confounding factors.

Several limitations must be acknowledged. The exact administration details of the first historical Dolo 650 exposure and the complete formulation of the intravenous paracetamol preparation were not independently verified. The first episode involved concurrent mesalamine administration, fasting, bowel preparation and hypotension. The cause of the postural blackout episodes remained uncertain. The immunological mechanism was not established through validated mechanistic testing. A contribution from formulation-specific excipients could not be completely excluded. The naproxen challenge employed approximately 15–20-minute inter-dose intervals, shorter than the EAACI/ENDA recommendations, and the exact duration of observation after the final dose was unavailable. Finally, delayed reactions and long-term tolerance during repeated naproxen exposure were not established.

The clinical findings should therefore be interpreted as confirming immediate hypersensitivity to the tested Dolo 650 preparation and supporting a selective paracetamol hypersensitivity phenotype rather than proving a specific immunological mechanism or establishing unrestricted tolerance to all other analgesics.

CONCLUSION

We report a case of clinically confirmed immediate hypersensitivity to Dolo 650 (paracetamol/ acetaminophen) in a patient with ulcerative colitis, demonstrated by objective urticaria during supervised oral DPT at a cumulative administered dose of 195 mg. A subsequent graded oral naproxen challenge demonstrated immediate tolerance to a cumulative dose of 650 mg under the documented test conditions, supporting a selective paracetamol hypersensitivity phenotype rather than generalized cross-reactive NSAID intolerance.

The case emphasizes the importance of careful clinical chronology, particularly when hypotension precedes exposure to the suspected culprit medication. It also illustrates the complementary roles of culprit-drug and alternative-drug provocation testing in confirming hypersensitivity and identifying potential therapeutic options.

In patients with underlying inflammatory bowel disease, a negative allergy challenge must be interpreted alongside broader considerations of gastrointestinal medication safety. Accurate clinical phenotyping, transparent reporting of challenge protocols and individualized decision-making remain central to contemporary EAACI/ENDA-aligned drug hypersensitivity practice.

REFERENCES

1. Barbaud A, Garvey LH, Torres M, et al. EAACI/ENDA position paper on drug provocation testing. *Allergy*. 2024;79(3):565–579. doi:10.1111/all.15996.
2. Doña I, Sáenz de Santa María R, Moreno EM, Bartra J, Torres MJ. An algorithm for the diagnosis and treatment of nonsteroidal antiinflammatory drugs hypersensitivity, 2024 update. *Allergy*. 2025;80(4):1183–1186. doi:10.1111/all.16349.
3. Romano A, Valluzzi RL, Alvarez-Cuesta E, et al. Updating the classification and routine diagnosis of NSAID hypersensitivity reactions: A WAO Statement. *World Allergy Organ J*. 2025;18(8):101086. doi:10.1016/j.waojou.2025.101086.
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(10):1219–1232. doi:10.1111/all.12260.
5. Kidon M, Blanca-Lopez N, Gomes E, et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. *Pediatr Allergy Immunol*. 2018;29(5):469–480. doi:10.1111/pai.12915.
6. Doña I, Pérez-Sánchez N, Bogas G, Moreno E, Salas M, Torres MJ. Medical algorithm: Diagnosis and treatment of nonsteroidal antiinflammatory drugs hypersensitivity. *Allergy*. 2020;75(4):1003–1005. doi:10.1111/all.14119.
7. Rutkowski K, Nasser SM, Ewan PW. Paracetamol hypersensitivity: clinical features, mechanism and role of specific IgE. *Int Arch Allergy Immunol*. 2012;159(1):60–64. doi:10.1159/000335213.
8. Blanca-Lopez N, Torres MJ, Doña I, et al. Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin Exp Allergy*. 2013;43(1):85–91. doi:10.1111/cea.12013.
9. Doña I, Barrionuevo E, Salas M, et al. NSAIDs-hypersensitivity often induces a blended reaction pattern involving multiple organs. *Sci Rep*. 2018;8(1):16710. doi:10.1038/s41598-018-34668-1.
10. Golden DBK, Wang J, Waserman S, et al. Anaphylaxis: A 2023 practice parameter update. *Ann Allergy Asthma Immunol*. 2024;132(2):124–176. doi:10.1016/j.anai.2023.09.015.
11. Wang J, Lieberman JA, Wallace DV, Waserman S, Golden DBK. Anaphylaxis in Practice: A Guide to the 2023 Practice Parameter Update. *J Allergy Clin Immunol Pract*. 2024;12(9):2325–2336. doi:10.1016/j.jaip.2024.06.036.
12. Li L, Bensko J, Buchheit K, Saff RR, Laidlaw TM. Safety, Outcomes, and Recommendations for Two-Step Outpatient Nonsteroidal Anti-Inflammatory Drug Challenges. *J Allergy Clin Immunol Pract*. 2022;10(5):1286–1292.e2. doi:10.1016/j.jaip.2021.11.006.
13. Mayorga C, Çelik GE, Pascal M, et al. Flow-based basophil activation test in immediate drug hypersensitivity. An EAACI task force position paper. *Allergy*. 2024;79(3):580–600. doi:10.1111/all.15957.
14. Cohen-Mekelburg S, Van T, Wallace B, et al. The Association Between Nonsteroidal Anti-Inflammatory Drug Use and Inflammatory Bowel Disease Exacerbations: A True Association or Residual Bias? *Am J Gastroenterol*. 2022;117(11):1851–1857. doi:10.14309/ajg.0000000000001932.
15. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case report guideline development. *J Clin Epidemiol*. 2014;67(1):46–51. doi:10.1016/j.jclinepi.2013.08.003.