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# WHEN "SAFE" ISN'T SAFE: CONFIRMED PARACETAMOL-INDUCED ANAPHYLAXIS DIAGNOSED BY DRUG PROVOCATION TESTING

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## ABSTRACT

Paracetamol (acetaminophen) can, in rare cases, induce anaphylaxis, and a drug provocation test (DPT) is considered the gold standard for diagnosis. However, due to the high risk involved with a life-threatening reaction, DPT is generally only performed under strict medical supervision when the history is unclear, and skin tests are inconclusive. Acetaminophen is the most commonly used antipyretic in children. However, there are limited data assessing hypersensitivity reactions related to acetaminophen usage. Paracetamol is a common antipyretic/ analgesic and a component of many prescription and over-the-counter preparations. Hypersensitivity reactions to paracetamol appear to be increasing, but there are few prevalence data.

**KEYWORDS:** Paracetamol; Acetaminophen; Drug hypersensitivity; Anaphylaxis; Drug provocation test; IgE-mediated reaction.

## INTRODUCTION

Acetaminophen has long been widely used as a primary treatment for mild-to-moderate pain, as an adjunctive analgesic to opioids in moderate-to-severe pain management, and as an antipyretic.[1]

Acetaminophen is considered to be quite safe, and cases of acetaminophen-induced anaphylaxis have been rarely reported.[2,3]

With the recent development and active administration of vaccines against coronavirus disease 2019 around the world, the Centers for Disease Control and Prevention advised that acetaminophen could be taken for fever caused by the vaccination.[4]

Therefore, the use of acetaminophen is expected to sharply and significantly increase. Accordingly, more attention should be paid to the potential risk of rare but serious adverse events of acetaminophen.[5]

Paracetamol anaphylaxis is a very rare event, with only a few cases described in the literature and even fewer reported in children.[6]

A patient suffering several episodes of anaphylaxis (generalized urticaria, dyspnea, wheezing, and intense cough) a few minutes after taking different drugs containing paracetamol.[7]

Acetaminophen (paracetamol--P) and Nimesulide (N) are widely used analgesic-antipyretic/anti-inflammatory drugs. The rate of adverse hypersensitivity reactions to these agents is generally low.[8]

Paracetamol is a common antipyretic/analgesic and a component of many prescription and over-the-counter preparations. Hypersensitivity reactions to paracetamol appear to be increasing, but there are few prevalence data.[9]

Drug hypersensitivity reactions represent a significant diagnostic and therapeutic challenge in clinical allergy practice[10]

Paracetamol is one of the most commonly used analgesics and antipyretic agents worldwide and is frequently recommended as a safer alternative to non-steroidal anti-inflammatory drugs[11]

## CASE PRESENTATION

A young adult woman was referred for evaluation of suspected drug hypersensitivity following recurrent acute reactions over several months. She experienced three reproducible episodes characterized by facial angioedema, generalized pruritus, and erythematous rash .Symptoms consistently developed within one hour of drug intake and resolved within approximately two hours.

All reactions were temporally associated with ingestion of paracetamol-containing medications, including combination cold preparations .Paracetamol was identified as the most likely common culprit drug based on exposure history and symptom reproducibility.

The patient had no prior history of asthma, allergic rhinitis, chronic spontaneous urticaria, food allergy, or previous anaphylaxis .No cofactors such as exercise, infection, or alcohol intake were identified preceding the reactions .Based on the clinical history, an immediate-type drug hypersensitivity reaction was strongly suspected.

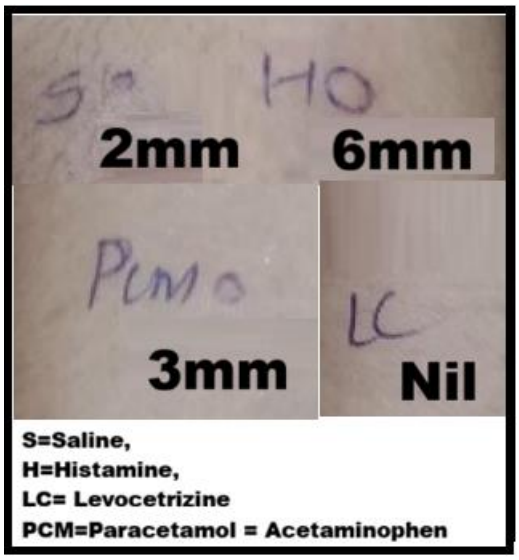
### Diagnostic Evaluation

Drug skin testing was performed as part of the diagnostic work-up, acknowledging its limited utility for paracetamol hypersensitivity.[12,13]

Skin testing for paracetamol yielded an equivocal response, while tests for alternative analgesics were negative.[14]

These findings were considered non-diagnostic due to the known low sensitivity and lack of validated concentrations for paracetamol skin testing[15]

In accordance with EAACI recommendations, a drug provocation test was planned to confirm or exclude true hypersensitivity

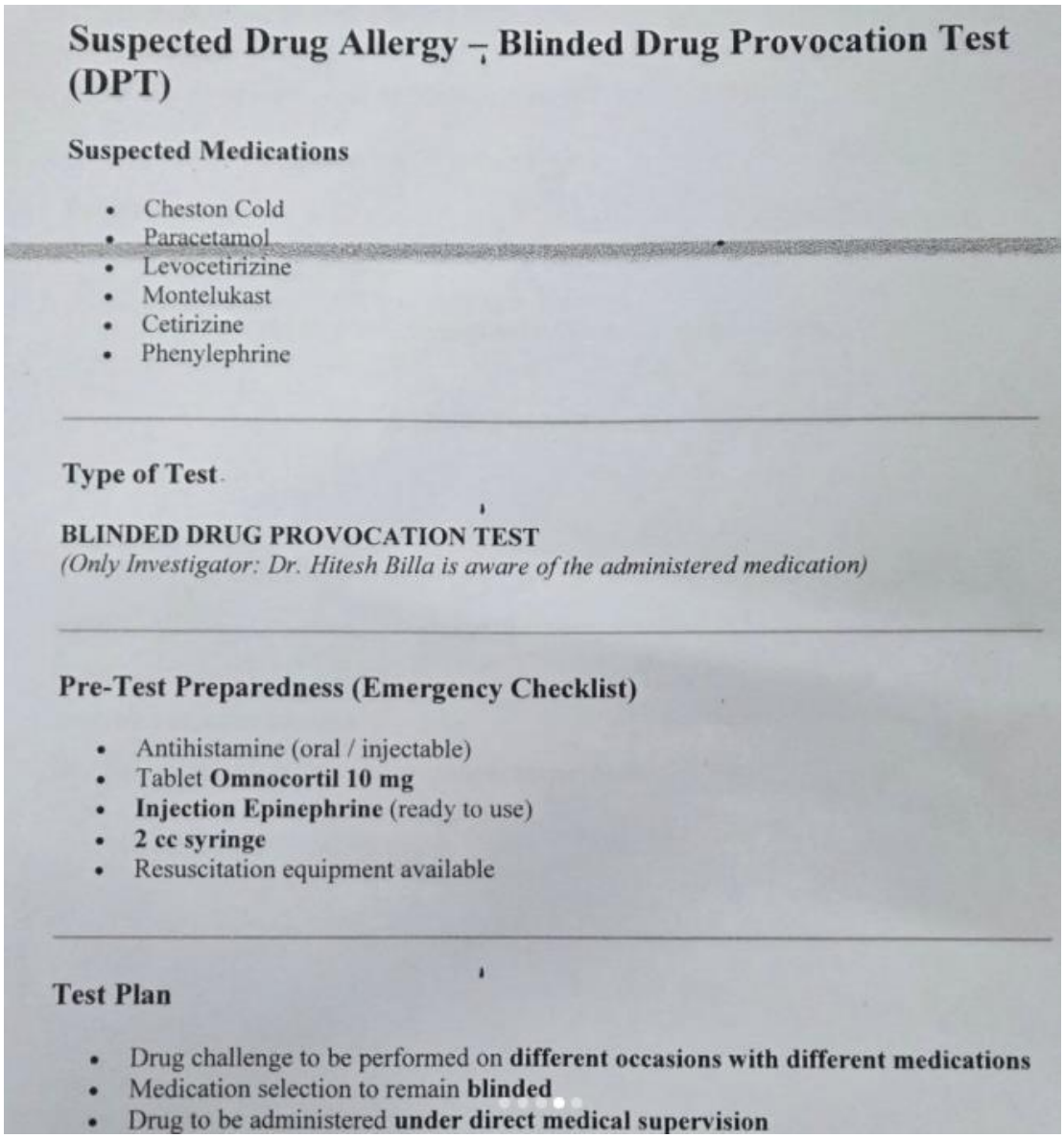



**Drug Provocation Test**

A blinded oral drug provocation test with paracetamol was performed in a hospital emergency setting with full resuscitation facilities available[16]

Written informed consent was obtained after detailed discussion of potential risks, including anaphylaxis.[8,14] The patient was fasting, clinically stable, and not receiving antihistamines or systemic corticosteroids at the time of testing[17]

Paracetamol (Revealed Patient after managing anaphylaxis, Tested Brand DOLO 650mg) was administered orally at a therapeutic dose under continuous medical supervision[18]



**Suspected Drug Allergy – Blinded Drug Provocation Test (DPT)**

**Suspected Medications**

- Cheston Cold
- Paracetamol
- Levocetirizine
- Montelukast
- Cetirizine
- Phenylephrine

**Type of Test**

**BLINDED DRUG PROVOCATION TEST**
*(Only Investigator: Dr. Hitesh Billa is aware of the administered medication)*

**Pre-Test Preparedness (Emergency Checklist)**

- Antihistamine (oral / injectable)
- Tablet **Omnocortil 10 mg**
- **Injection Epinephrine** (ready to use)
- **2 cc syringe**
- Resuscitation equipment available

**Test Plan**

- Drug challenge to be performed on **different occasions with different medications**
- Medication selection to remain **blinded**
- Drug to be administered **under direct medical supervision**

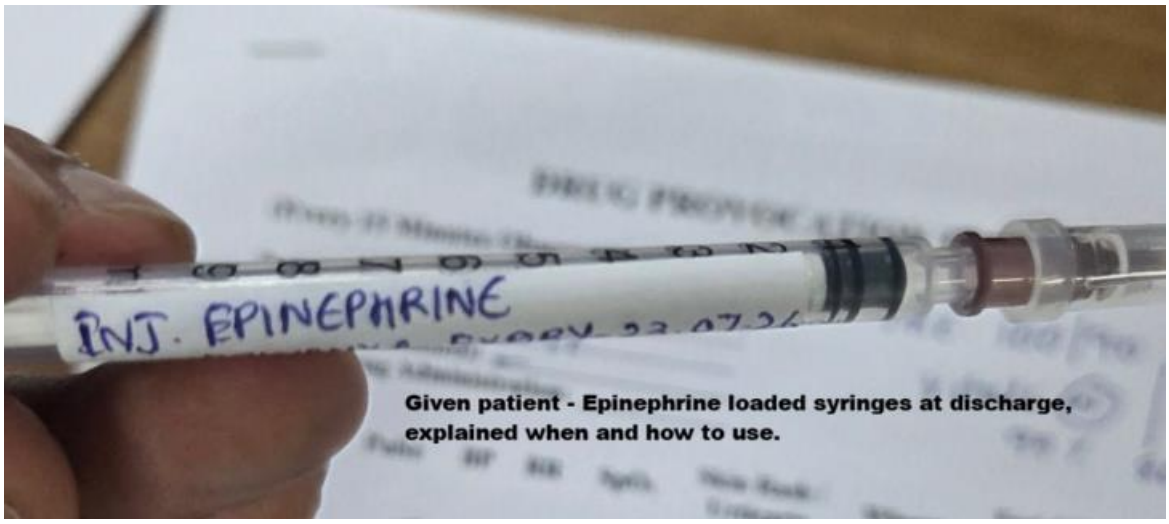
**Adverse Reaction and Management**

Within minutes of drug administration, the patient developed generalized urticaria, intense pruritus, and facial angioedema.[19]

She additionally experienced rhinitis, chest discomfort, and respiratory symptoms consistent with systemic involvement[20]

The clinical presentation fulfilled established diagnostic criteria for anaphylaxis. Immediate treatment with intramuscular adrenaline was administered, followed by intravenous corticosteroids.[21]

The patient responded promptly to treatment and achieved complete clinical stabilization under close observation No biphasic or protracted anaphylactic reaction was observed during the monitoring period.[22] The patient was observed for 24 hours and discharged in stable condition the following day.




## DISCUSSION

Hypotensive shock or anaphylaxis caused by acetaminophen is rare, but several reports have described cases of acetaminophen-induced anaphylaxis.

### Final Diagnosis

A final diagnosis of **confirmed IgE-mediated paracetamol (acetaminophen)–induced anaphylaxis** was established based on a positive drug provocation test .Alternative diagnoses such as non-immunological intolerance or idiopathic urticaria were excluded by objective reaction during controlled exposure.

### Management and Follow-Up

The patient was advised permanent and absolute avoidance of paracetamol and all paracetamol-containing combination medications.[23]

She was prescribed an adrenaline auto-injector and provided with a written anaphylaxis action plan. Education was given regarding early recognition of anaphylaxis and the importance of prompt adrenaline administration. Such preventive strategies are essential to reduce morbidity and prevent fatal outcomes in drug-induced anaphylaxis.

### Ethical and Legal Considerations

Written informed consent was obtained prior to drug provocation testing in accordance with international guidelines. Separate consent was obtained for anonymous publication of clinical data. Clinical photographs were intentionally not obtained, as the patient was in significant distress during the acute reaction, and omission avoided interference with emergency management.

No identifiable patient information is included in this report, ensuring compliance with ethical and medico-legal standards.

## CONCLUSION

Paracetamol-induced anaphylaxis, although rare, represents a potentially life-threatening condition .Clinical history remains the cornerstone of suspicion, while drug provocation testing provides definitive diagnosis when safely performed. Early recognition and accurate labeling are essential to prevent repeated exposure and severe outcomes .

Future studies assessing the risk of immediate and nonimmediate hypersensitivity reactions to acetaminophen and elucidating the mechanism of acetaminophen hypersensitivity reactions are required.

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