



Case Reports

Challenges in Diagnosing Pantoprazole-Induced Drug Fever: A Case Report in a Critically Ill Patient

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Abstract

Drug fever remains a diagnostic challenge in clinical practice. Proton pump inhibitors (PPIs), like pantoprazole, are rarely implicated in drug fever cases despite their widespread use. We present a case of a 56-year-old man hospitalized for acute hematemesis, who developed persistent fever despite antimicrobial therapy. Fever resolved rapidly upon discontinuing pantoprazole, confirming pantoprazole-induced drug fever. This case highlights the diagnostic complexities of drug fever in critically ill patients and underscores the importance of considering less commonly suspected agents like pantoprazole to avoid unnecessary treatments and prolonged hospitalizations.

BACKGROUND

Drug fever is a febrile reaction caused by the initiation of a drug and resolves after discontinuation of the drug when no other explanation of the fever is available.¹ It is a diagnosis of exclusion, requiring careful examination of the patient's fever pattern, medications, lab studies, physical exam, and comorbidities. Although clinicians are aware that drugs can cause adverse reactions, fever as the sole manifestation occurs in an estimated 3-5% of cases, often leading to misdiagnosis and underreporting.² Diagnosing drug fever is challenging and often mistaken for infections, resulting in expensive workups, overuse of antimicrobials, unnecessary hospital admissions, and prolonged hospital stays. One study showed that an episode of drug fever extends the hospital stay by an average of 8.7 days, involves a mean of 5 blood cultures, 2.85 radiologic imaging studies, and the increased use of antibiotics, antipyretics, and steroids.³

Due to the impracticality of conducting clinical trials on drug fever, understanding is largely based on adverse reports and case studies.² Common agents for drug fever include antimicrobials, anticonvulsants, antiarrhythmics, immunoregulators, and antineoplastics.^{1,4} Proton pump inhibitors (PPIs) are not commonly associated with drug fever. To our knowledge, there have been only a few case reports of drug-induced fever caused by PPIs, including esomeprazole and pantoprazole.⁵⁻⁷ Given the frequent prescription of PPIs for gastrointestinal ulcers and acute GI bleeding in both outpatient and inpatient settings, awareness of PPI-induced drug fever is crucial for diagnosing fever of unknown origin. We present a case of a 56-year-old man with a complicated cardiac history who

developed an intermittent fever over 17 days while on pantoprazole.

CASE PRESENTATION

A 56-year-old man with a history of type 2 diabetes, hypertension, nonischemic dilated cardiomyopathy (EF=25%), atrial fibrillation on warfarin and amiodarone, sleep apnea, and a remote history of Roux-en-Y presented to the emergency department with acute hematemesis. He received 2000 units of KCENTRA, pantoprazole 80 mg/100mL infusion, and octreotide drips. Upper endoscopy revealed a large ulcer at the gastrojejunal anastomosis site. He was admitted to the ICU and was intubated for airway protection in setting of hematemesis and hypoxic respiratory failure. A central line was placed via the left subclavian approach. He was started on ceftriaxone and doxycycline, which were switched to piperacillin-tazobactam and vancomycin on day 2 for suspected left lower lobe pneumonia indicated by chest X-ray. Octreotide drips were discontinued on day 2, but pantoprazole infusion continued.

The patient remained afebrile initially, with a peak white count of $26.6 \times 10^9/L$ (reference range: $4.2 - 10.0 \times 10^9/L$), which decreased on antibiotics. On day 5, he developed a fever of 100.9°F while on piperacillin-tazobactam and vancomycin. He was switched to empiric meropenem for ventilator-associated pneumonia and micafungin was started for possible gut translocation due to GI bleed. On day 7, pantoprazole infusion was changed to pantoprazole injection 40 mg BID. A thorough workup, including MRSA screening, respiratory panel, blood cultures, 1,3-beta-D-glucan, stool *C.difficile* PCR,

and urinalysis, were all negative, and the white count normalized. However, the fever persisted, peaking at 103°F on day 8.

On day 9, the patient's condition was further complicated by the development of lobar pulmonary emboli, requiring heparin infusion, and a ventricular fibrillation arrest with return of spontaneous circulation (ROSC). Amiodarone was discontinued due to concerns about QT prolongation, and lidocaine was initiated. On day 12, meropenem and micafungin were discontinued after completing their respective courses (7 days for meropenem and 5 days for micafungin). From days 13 to 19, the patient was not on any antimicrobials. Despite normal CBC, including white count and eosinophils, he continued to experience fevers, peaking at 101.3°F. His heart rate fluctuated between the 70s and 130s. An extensive infectious workup, including varicella-zoster virus (VZV) PCR of a right thigh vesicle, urine cultures, and sputum cultures, all returned negative. CRP was elevated at 84.40 mg/L (reference range: 0.00 - 10.00 mg/L).

On day 20, the patient was pan cultured again given persistent fever and lack of clear infectious source. The urinalysis showed 3+ leukocyte esterase, >180 WBCs, and negative nitrite in the setting of multiple urinary catheter placements. Meropenem started for possible urinary tract infection. Urine culture grew *Klebsiella pneumoniae* resistant to ampicillin and nitrofurantoin and susceptible to all other antibiotics tested. Further imaging, including CT scan of abdomen and pelvis, was negative. While on meropenem, the patient remained febrile. Given the normal WBC count and the unrevealing CT scan of abdomen and pelvis, drug fever was considered, with possible culprits being meropenem and pantoprazole. On day 22, meropenem was switched to IV trimethoprim-sulfamethoxazole for the UTI, and pantoprazole was switched to lansoprazole. Within 48 hours of discontinuing meropenem and pantoprazole, the patient's fever subsided as illustrated in figure 1. He was transferred to the general ward on day 23 for monitoring of fevers, CHF exacerbation, and delirium - all of which subsequently resolved. He remained afebrile until discharge to a skilled nursing facility on day 39.

DISCUSSION

In this case, the diagnosis of drug fever due to pantoprazole was supported by the temporal relationship between fever onset and pantoprazole administration, the absence of alternative causes, and the resolution of fever within 72 hours of discontinuation.⁴ Though meropenem was initially considered as another potential cause of drug fever, its discontinuation on day 12 did not result in fever resolution, suggesting that pantoprazole-induced drug fever was more likely in this patient. Literature indicates that the onset of drug fever is highly variable, typically occurring with a median lag time of 7-10 days after initiation

of the offending drug in nonsensitized individuals, and resolves within 48-72 hours of discontinuation.^{2,8} Our case aligns with these temporal patterns, with fever onset observed on day 5 following pantoprazole initiation and subsequent resolution within 48 hours of discontinuation, consistent with findings reported by Melo et al. regarding pantoprazole-induced drug fever.⁷

Furthermore, our patient's clinical presentation parallels Mackowiak's review, highlighting that contrary to textbook descriptions, drug fever often lacks classical features such as relative bradycardia, rash, or eosinophilia.¹ During the fever episodes, our patient exhibited fluctuating heart rates ranging from the low 70s to 130s without accompanying dermatological manifestations typical of drug rash or eosinophilia. Notably, his CRP levels were markedly elevated at 84.40 mg/L (reference range: 0.00 - 10.00 MG/L), resembling findings reported in other case studies of pantoprazole-induced drug fever.^{6,7} However, elevated CRP levels alone do not narrow down diagnostic differentials, as they can also indicate various other conditions including infections, inflammations, and malignancies. Regarding fever pattern, our patient experienced intermittent spikes in fever every day for 17 days, beginning 5 days after initiation of pantoprazole, with temperatures fluctuating between a maximum of 103°F and a minimum of 97°F throughout each day. According to the literature, fever patterns in drug fever are highly variable. They can manifest as continuous or intermittent, ranging from low-grade fevers around 99°F to high fevers up to 109°F, which presents an additional challenge in diagnosing drug fever based on fever pattern.²

Diagnosing drug fever in critically ill ICU patients is particularly challenging due to the need to rule out numerous potential causes of fever of unknown origin. These patients, including ours, are at heightened risk of infections given invasive procedures such as intubation, central line placement, and urinary catheterization. Early in his ICU stay, our patient exhibited signs suggestive of pneumonia, including a chest X-ray showing left lower lobe consolidation and an elevated white blood cell count, indicative of an initial infectious process. However, the persistence of fever beyond antibiotic treatment and despite normalized white blood cell counts while on meropenem raised suspicion for drug fever rather than ongoing infection. Similarly, despite testing positive for *Klebsiella pneumoniae* UTI on day 20, our patient maintained a normal white blood cell count and was on appropriate antimicrobial therapy with meropenem, making drug fever a more likely cause of his persistent fever than the UTI itself. In addition, His pulmonary emboli present another possible cause of fever of unknown origin; however, pulmonary embolism rarely results in a fever lasting more than a week, particularly if the temperature exceeds 101.3°F.⁹ Given that our patient experienced intermittent daily fever spikes for 17 days, it is highly unlikely that the fever is solely attributable to pulmonary



Figure 1. Fever Curve Indicating Temperature and WBC Count Trends in an ICU Patient with Fever of Unknown Origin, Later Diagnosed as Pantoprazole-Induced Drug Fever.

This figure displays the patient's temperature and white blood cell (WBC) count from March 29 to April 5. Pantoprazole was discontinued on April 2, and within 48 hours, the patient's fever resolved.

embolism. Notably, malignancy-related fever was effectively ruled out by negative findings on a CT scan of abdomen and pelvis.

This case highlights the complexity of diagnosing drug fever in critically ill patients and emphasizes the need for a comprehensive diagnostic approach. According to Mourad et al.'s systematic review, fever of unknown origin poses a diagnostic challenge in hospitalized patients, and early investigation should include ruling out drug fever by reviewing and discontinuing or replacing potential culprit medications if feasible.¹⁰ However, in ICU settings, discontinuing essential medications is often impractical, making it crucial for clinicians to maintain a heightened awareness of drug fever as a potential adverse event associated with certain medications. When multiple medications are suspected, prioritizing discontinuation based on suspicion level is recommended. Subsequent reintroduction of essential medications should be approached sequentially, starting with those deemed less likely to be causative.

Delays in diagnosing drug fever can lead to extensive and costly investigations, prolonged hospital stays, and unnecessary antimicrobial use.³ Our case report aims to raise awareness of drug fever, a frequently underdiagnosed and misdiagnosed condition, particularly in medications not typically associated with such reactions, like PPIs. While generally well-tolerated, PPIs, including pantoprazole, have reported fever as a common (>4%) adverse reaction in pediatric patients and have been implicated in a few drug fever cases in adults, possibly due to their

ability to cross the blood-brain barrier and interfere with hypothalamic temperature regulation.^{5,6,11} Additionally, esomeprazole and pantoprazole exhibit higher plasma concentrations and enhanced tissue delivery compared to other PPIs, potentially contributing to their association with drug fever.⁵ This adverse effect appears to be dose-dependent, which could explain why these specific PPIs are implicated while others are not.⁵ Further pharmacokinetic studies are warranted to elucidate why certain PPIs, such as pantoprazole and esomeprazole, exhibit a higher propensity for causing drug fever compared to others within the class.

In conclusion, this case report highlights the importance of including drug fever in the differential diagnosis of fever in hospitalized patients, especially in critically ill patients, particularly with less commonly suspected agents like pantoprazole, in order to avoid unnecessary diagnostic procedures and potentially harmful treatments.

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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