



Drug Fever: Recent Cases from the Medical Literature

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Drug fever is conventionally defined as a fever above 38° C occurring after drug administration, without other potential causes, that ceases within 72 hours after drug discontinuation. Other symptoms may include chills, fatigue, and relative bradycardia (a lack of increase in heart rate in the presence of fever). Some definitions include the presence of a rash, while others exclude dermatologic symptoms. Laboratory testing may reveal thrombocytopenia, neutropenia, eosinophilia, increased aminotransferases, or an increased erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), although the presence of these results are not necessary to establish the diagnosis.^{1,2} Drug fever is a diagnosis of exclusion and requires a thorough investigation for other causes of fever, including infection, recent surgery or trauma, malignancy, thromboembolic disease, collagen vascular diseases, gout, serum sickness-like reactions, serotonin syndrome, neuroleptic malignant syndrome, or malignant hyperthermia. The diagnosis of drug fever is challenging, and is particularly difficult when the patient is receiving the drug to treat a disease which presents with a fever. While a positive re-challenge can aid in confirming the diagnosis, it is not recommended due to the potential risk to the patient.

Incidence

It has been estimated that drug fever accounts for less than 5% of drug-related adverse effects. This is likely lower than the actual frequency due to misdiagnosis and underreporting.¹ Determining causality, the probability that the suspected drug produced the adverse reaction, is also difficult in these cases, particularly when multiple drugs are in use at the time of fever onset.

One of the most useful resources on drug fever was published by Vodovar and colleagues in 2012.² The authors conducted a descriptive cohort study of the French National Pharmacovigilance

Database, which included 167 cases of drug fever involving 115 drugs reported between 1986 and 2007. The median age of the patients was 52 years, with 16% of the cases occurring in patients less than 18 years of age. Using the Naranjo adverse drug reaction probability scale, in 55 of the cases causality was considered possible, while 78 were probable and 33 were definite. The median time from drug administration to onset of fever was 2 days [1.0-10.5], with a median peak fever of 39° C [38.7°-39.8°]. A continuous fever was reported in 52% of cases, with an intermittent fever in 48%. The median time from the onset of fever to drug discontinuation was 3 days [1.0-11.5]. Other signs or symptoms were uncommon, with chills in 15% of patients, fatigue in 3.4%, an increased CRP in 8.9%, elevated aminotransferases in 8%, neutropenia in 0.9%, and eosinophilia in 0.9%. A drug re-challenge, performed in 38% of the reports, resulted in a recurrence of symptoms in all cases. Hospitalization or a prolonged hospital stay was reported in 24.5% of the cases, but a life-threatening event was reported in only one patient. There were no deaths associated with drug fever in this cohort, but fatalities have been described in earlier studies.³

The findings from the French study are similar to those reported in a 2016 analysis of 16 cases of antibiotic-related drug fever seen by the infectious disease consultants at Japan's Kurume University Hospital.⁴ The most common agents in this retrospective analysis were vancomycin, teicoplanin (another glycopeptide), and piperacillin-tazobactam. The mean time from initial administration of the drug and the onset of fever was 8.6 ± 5.3 days, with an interval between discontinuation and fever resolution of 3.4 ± 3.3 days. The mean peak temperature was 38.8 ± 0.8° C, with most patients experiencing a gradual rise. The peak white blood cell (WBC) count was 7.5 ± 3.6 x 10⁹/L, with a peak CRP of 5.1 ± 3.9

mg/dL. Procalcitonin levels were assessed in 10 patients, with only one having a significantly elevated level (> 0.25 ng/dL).

Potential Mechanisms

The mechanisms for development of drug fever are not fully understood. It is likely that multiple pathways are involved, based on the structure and function of the causative agent.^{1,2} Among the potential mechanisms suggested to date are 1) alteration of normal regulation of body temperature by the drug, such as that seen with sympathomimetics, levothyroxine, tricyclic antidepressants or antipsychotics, 2) pyrogenic contaminants or components of certain drug products, such as amphotericin B or bleomycin, 3) fever associated with drug administration, as with vaccines, or fever resulting from phlebitis after drug injection or infusion, 4) release of endotoxins or lipopolysaccharides following destruction of bacterial cell walls by antibiotics or cytokine release after chemotherapy, 5) idiosyncratic reactions in genetically predisposed patients, such as those seen with anesthetic agents, haloperidol, or sulfonamides, or 6) hypersensitivity reactions caused by antimicrobials, carbamazepine, heparin, phenytoin, quinidine, or sulfonamides.

Anti-infective agents are the most frequently reported cause of drug fever. In the French National Pharmacovigilance Database study, 68% of the cases involved an anti-infective agent.² The most commonly reported drugs in that study were amikacin, oxacillin, cefotaxime, ceftriaxone, rifampin, and vancomycin. The authors pointed out that this may not reflect a greater propensity for anti-infective drugs to cause drug fever, but instead that a more in-depth evaluation for other causes may lead to increased reporting.

Recent Case Reports

Acitretin

In 2015, Rob and colleagues reported the first case of acitretin-induced drug fever in a patient being treated for psoriasis.⁵ Acitretin is a retinoic acid analog that modulates epidermal proliferation and differentiation. The most commonly reported adverse effects associated with its use are cheilitis, xerosis, and alopecia. Although fever is not a typical adverse effect of acitretin, in this case report the patient became febrile within 24 hours of initiation of low-dose therapy (25 mg/day). Intermittent fevers, up to 38.8° C, continued to occur every day while the patient was evaluated and treated for a presumed infection. After finding no other source, acitretin was discontinued on day 10 of therapy. The following day, the patient was afebrile. On follow-up there was no return of the fever. The authors postulated that the patient had drug fever caused by a hypersensitivity reaction.

They note that the patient's relative bradycardia (a heart rate not exceeding 75 bpm) in the face of hyperthermia supports the diagnosis.

Anti-tuberculosis Treatments

Fang and colleagues recently published a review of 78 cases of drug fever in patients being treated for pulmonary tuberculosis at the Shanghai Pulmonary Hospital.⁶ The patients ranged in age from 9 to 87 years of age (mean 41 years). Rifampin was the cause of 45% of the cases reported, followed by para-aminosalicylic acid in 14%, rifabutin in 9%, and pyrazinamide in 7%. Eleven patients had fevers with more than one drug. Most patients (93%) developed a fever within 3 weeks of starting treatment. Forty percent had fevers greater than 39° C. Additional symptoms included chills, headache, rhinitis, nausea, vomiting, rash, and joint pain. Eosinophilia occurred in 15 patients (16%). Ten patients of the 63 tested had elevated transaminases, with four having evidence of hepatic disease. The drug considered to be the cause was immediately discontinued in 59 cases, with a gradual withdrawal in the rest. Because of the risks associated with untreated tuberculosis, the authors recommend immediate discontinuation of only one drug at a time, beginning with the most likely cause.

Dalteparin

In 2016, Wackernagal and colleagues described drug fever in a premature neonate being treated with dalteparin.⁷ The patient, born at 26 weeks gestational age, began treatment with dalteparin (100 units/kg twice daily by subcutaneous injection) on day of life 5 for a right ventricular thrombus. The fever started two days later, along with signs of discomfort and tachycardia. The temperature in the incubator was adjusted to maintain normothermia. Once infection had been excluded as a potential cause on day of life 17, dalteparin was discontinued and heparin was initiated. The neonate soon returned to a normal temperature and heart rate. On day of life 22, anticoagulation was changed back to dalteparin. Two days later, the patient once again became febrile, irritable, and tachycardic. Dalteparin was again stopped on day of life 26, with prompt symptom resolution. This reaction was unexpected, as the most likely underlying mechanism, a hypersensitivity reaction, is uncommon in infants due to the immaturity of the immune system. The authors suggest that this may represent an idiosyncratic reaction or a local reaction to the injection. The Naranjo scale estimated the causality as probable, while the Liverpool Adverse Drug Reaction Causality Assessment Tool rated it as definite. While more than 50 cases of dalteparin-induced drug fever have been reported worldwide, this case is believed to be the first reported in a neonate.

Dexmedetomidine

Nine cases of dexmedetomidine-induced drug fever were reported by Krüger and colleagues in *Anesthesia and Analgesia* earlier this year.⁸ The cardiac intensive care patients (median age 67 years) received dexmedetomidine beginning on postoperative day 1. Hyperthermia occurred at a median time of 6 hours after starting therapy (interquartile range 4-10 hours) at a median dexmedetomidine dose of 1 mcg/kg/hr (0.8-1.3 mcg/kg/hr). The median maximum body temperature was 39° C (38.8-39.2° C). Administration of acetaminophen or use of a cooling device failed to return any of the patients to normothermia. The median time to drug discontinuation was 26 hours (9-35 hours), with a median time to normothermia of 4 hours (3-9 hours). Dexmedetomidine was discontinued because of drug fever in only three of the patients. Two patients were treated with dexmedetomidine a second time, with only one experiencing hyperthermia during the second treatment period. While the patients were receiving multiple drugs during the period in which they were hyperthermic, a temporal relationship was only demonstrated with dexmedetomidine.

Ertapenem

Carbapenem-induced drug fever has not often been reported, but a recent case involving ertapenem suggests that these drugs can be a potential source.⁹ The patient, a 91-year-old woman, was placed on ertapenem (1 gram/day) for pneumonia and a urinary tract infection that had failed to respond to treatment with ceftriaxone and azithromycin. She became afebrile shortly after the change in therapy, with an improvement in her alertness. On day 10 of therapy, her temperature rose to 39.2° C without a change in her clinical status, physical exam, chest X-rays, or laboratory tests. Drug fever was suspected and ertapenem was discontinued, with resolution of the fever within 2 hours. Assessment with the Naranjo scale suggested probable causality. The author noted that the diagnosis in this case was supported by the temporal association with onset of fever, the lack of another cause of the fever, and the rapid return to normothermia after discontinuation.

Minocycline

In a brief report published earlier this year, Gu and colleagues described drug fever without a rash in a 24-year-old patient being treated with oral minocycline (100 mg/day) for acne. The patient developed a fever to 39.5° C, fatigue, dizziness, eye pain, and chest tightness on day 6 of treatment. After presenting to the hospital, she was diagnosed with a cold and a potential reaction to minocycline. The drug was discontinued, but the fever and fatigue continued for another 5 days. Three days after the symptoms cleared,

minocycline was resumed. Within hours, the symptoms recurred with a fever of 39.2° C. The authors were consulted to evaluate a possible allergic reaction and noted normal vital signs, no rash, and no swollen or enlarged lymph nodes. The patient had eosinophilia (WBC 7.5 x 10⁹/L, eosinophils 1.2%) with a normal CRP. Blood cultures were negative. Minocycline was again discontinued and prednisone (30 mg/day) was started. Assessment with the modified Karch-Lasagna algorithm suggested definite causality. The rapid return of fever upon re-challenge further supports the diagnosis and highlights the risk of resuming the drug.

Pantoprazole

In 2014, Schiller and colleagues described a rare case of drug fever following a single dose of pantoprazole.¹¹ The patient, a 74-year-old woman, was admitted to the hospital after 8 hours of fever (maximum 38.9° C) and shivering following a 40 mg dose of pantoprazole. She reported similar symptoms with previous doses. She was otherwise in good health and had no other recent changes in her medications. In addition to hyperthermia, the patient had an elevated WBC (20 x 10⁹/L) and CRP (9.8 mg/dL). No eosinophilia was noted. Within 24 hours, the patient was afebrile and her laboratory tests were normal. She consented to a re-challenge and 15 hours after receiving a 40 mg pantoprazole dose again developed a headache and a fever (38.8° C), along with a similar increase in WBC and CRP. She was later successfully treated with esomeprazole. With the positive re-challenge and the lack of an immune-mediated response, the authors categorized this as an idiosyncratic reaction.

Piperacillin-Tazobactam

Penicillins and cephalosporins are among the drugs most commonly associated with drug fever.¹²⁻¹⁴ In the past several years, a growing number of case reports have involved piperacillin-tazobactam. Swe and colleagues described a case of drug fever in a 63-year-old male with HIV receiving piperacillin-tazobactam (2.25 grams every 6 hours) for acute cholecystitis.¹⁴ On day 3 of treatment, his temperature rose to 39.4° C. He continued to have intermittent fevers which were unresponsive to acetaminophen. He had no symptoms other than a relative bradycardia, with a heart rate of 80-90 bpm while febrile. There was no rash or eosinophilia. After ruling out infection, the drug was discontinued. The patient's temperature returned to normal within 48 hours with no recurrence.

Propofol

While multiple cases of drug fever due to anesthetics have been reported, most have involved inhalational agents. In 2015, Yatabe and

colleagues described the first case of propofol-induced drug fever in a patient undergoing hepatic segmentectomy.¹⁵ Anesthesia was induced with propofol, fentanyl, and rocuronium, followed by sevoflurane for maintenance. Her temperature was normal at the time of transfer to the intensive care unit and the initiation of propofol (1.8 mg/kg/hr) and dexmedetomidine (0.4 mcg/kg/hr) for sedation. Two hours later, her temperature was 39.5° C; and 14 hours after surgery, she remained febrile with an elevated WBC of 7.4 x 10⁹/L and a CRP of 2.9 mg/dL. The fever persisted, resulting in the patient being evaluated for pneumonia and treated with antibiotics. Throughout this period, she exhibited a relative bradycardia, with a heart rate of 75 bpm in spite of her elevated temperature. After 5 days with no change in her status, drug fever was suspected and propofol was discontinued. Her temperature decreased to 36.1° C within 3 hours. The authors conducted a thorough investigation of alternative causes for the fever, including the potential for other drugs to have been the cause. The temporal association, along with the relative bradycardia, support their diagnosis of propofol-induced drug fever.

Trimethoprim-Sulfamethoxazole

In a case report published earlier this year in *Cureus*, Vaisha and colleagues describe a 58-year-old patient with trimethoprim-sulfamethoxazole-induced drug fever. The patient was admitted for total hip arthroplasty. He had human immunodeficiency virus and advanced osteoarthritis of the left hip. He had an uneventful postoperative period, and at 72 hours his IV antibiotics were discontinued and oral clarithromycin and trimethoprim-sulfamethoxazole were started for prophylaxis of *Mycobacterium avium* complex. He became febrile on postoperative day 8, with a peak temperature of 39.4° C. An extensive evaluation for infection was initiated with addition of IV antibiotics. The fevers persisted, and on postoperative day 15, a diagnosis of trimethoprim-sulfamethoxazole-induced drug fever was proposed. The drug was stopped and the patient became afebrile over the next 48 hours.

Summary

Drug fever should be considered in any patient who continues to be febrile after infectious etiologies or other disease states associated with fever have been ruled out. Although drug fever rarely leads to serious medical complications, the suspected drug should be discontinued as soon as possible. Most patients will have resolution of their fever within 3 days after discontinuation. Ruling out other causes and confirming the diagnosis of drug fever, however, is often difficult and can lead to a prolonged length of hospital stay and increased healthcare costs. The growing literature on drug fever may assist in making the

diagnosis. Healthcare providers are encouraged to report cases to the MedWatch program www.fda.gov/Safety/MedWatch/default.htm and consider submitting them for publication to add to our understanding of this challenging adverse drug reaction.

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