

Case Report

Cefazolin-Related Fever in Postoperative Spine Surgery: A Case Report

Sirichai Wilatratsami MD*,
Pinpilai Jutasompakorn MD**, Panya Luksanapruksa MD*

* Department of Orthopedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

** Department of Pharmacology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: There have been few reports describing antibiotic related fever, especially in the beta-lactam class of antibiotics. The present report is a case of postoperative immediate-onset cefazolin-related fever in a lumbar spine surgery patient.

Case Report: A 58-year-old woman presented with progressive low back pain and neurogenic claudication of both extremities for six months. Magnetic resonance images (MRI) of the lumbar spine indicated central canal stenosis with nerve root compression from L4 to S1. After decompressive laminectomy, pedicular screw fixation, and posterolateral fusion were performed, the patient experienced postoperative fever without obvious evidence of infection. The blood and tip of drain bacterial culture grew no organisms. After prophylactic cefazolin was discontinued in postoperative day 5, the fever began to decline and returned to normal on postoperative day 9.

Conclusion: Postoperative drug fever that is caused by prophylactic cefazolin may be delayed in diagnosis because drug fever is usually diagnosed by exclusion after the elimination of other potential causes. The research authors would like to encourage physicians to be aware of this entity. Prompt cause identification can obviate unnecessary diagnostic procedures and inappropriate treatments.

Keywords: Drug fever, Cefazolin, Cephalosporin, Adverse event, Spine surgery

J Med Assoc Thai 2014; 97 (Suppl. 9): S144-S148

Full text. e-Journal: <http://www.jmatonline.com>

Postoperative fever that is common in the first few days after surgery, especially after a major operation^(1,2) is generally caused by inflammatory stimulus from the stress of surgery and frequently resolves itself spontaneously⁽³⁾. Differential diagnosis of postoperative fever includes infectious and non-infectious conditions such as wound sepsis, atelectasis, urosepsis, drug fever, thrombophlebitis, and deep vein thrombosis. Drug-related fever is most common after administration of antibiotics, especially in the beta-lactam class, and usually is resolved within 1 to 2 days after the termination of the drug. Cefazolin is the most common prophylactic antibiotic used in orthopedic surgery, including spine surgery. To our knowledge, there has been only one previously reported case in English research literature⁽⁴⁾. While most occurrences of postoperative cefazolin-related fever have delayed onset after first administration, this report

describes the first case of cefazolin-related fever in postoperative lumbar spine surgery in Thailand, in which the fever developed immediately after first administration of the drug.

Case Report

A 58-year-old woman presented with progressive low back pain and neurogenic claudication of both extremities for 8 months. Past medical history revealed no underlying disease or drug allergy. At the time of admission, physical examination showed pinprick sensation impairment at both sides of L5 and S1 dermatome. According to Medical Research Council scale, motor strength was graded 4/5 in the extensor hallucis longus and flexor hallucis longus on both sides of the body. The patient's muscle tone, anal sphincter tone, and deep tendon reflex were normal. Pre-operative laboratory tests showed white blood cell count to be 4,970/mm³ with 44.3% neutrophils and 0.8% eosinophils. The lateral view of the lumbar spine radiograph showed decreased disc space and spondylolisthesis at the L4-5 and L5-S1 levels. Sagittal lumbar magnetic resonance images (MRI) showed spinal stenosis from hypertrophy of the ligamentum

Correspondence to:

Luksanapruksa P, Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, 2 Prannok Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: 0-2419-7969

E-mail: panya.luk@mahidol.ac.th

flavum, with compressed nerve roots at the levels of L4 to S1 in T2 weighted MRI. Cefazolin was administered as prophylactic antibiotic. Intra-operative findings revealed venous congestion at the Para vertebral muscles. Lateral recess and foraminal stenosis from hypertrophy of the ligamentum flavum was found. Decompressive laminectomy and posterolateral fusion with local bone graft secured by pedicular screw system was performed at the levels of L4 to S1.

After surgery the patient had a fever of 39 degrees Celsius on postoperative day 1 (Fig. 1). The routine postoperative program was initiated, including early ambulation and breathing exercises using triflow spirometer. On postoperative day 2, the patient still had a fever, which ranged from 38-38.5 degrees Celsius. The surgical wound was normal and no discharge was found. No skin rash was developed. Laboratory tests showed the white blood cell count was 15,300/cumm with 84.2% neutrophils and 0.4% eosinophils. Urinalysis result had WBC 0-1 cell/HP and RBC 0-1 cell/HP. Serum C-reactive protein (CRP) concentration was 13.81 mg/L. Erythrocyte sedimentation rate (ESR) was 80 mm/hour. No bacterial growth was reported from blood, urine, and tip of drain cultures. Chest radiographic study showed no evidence of pneumonia. Duplex scan showed no deep vein thrombosis. The infectious disease consultation team recommended discontinuing the cefazolin. On that recommendation the cefazolin was terminated on the morning of postoperative day 5.

At this point in time, the patient's temperature was 38.2 degrees Celsius. On postoperative day 7, the patient's temperature continued to decline. The patient remained afebrile for the next 24 hours and was discharged on the morning of postoperative day 9.

Discussion

Drug fever is the febrile response that temporally coincides with the administration of a drug, which then disappears after discontinuation. The true incidence of drug fever is unknown, but it has been estimated to occur in approximately 10% of inpatients⁽⁵⁾. Drug fever should be considered in the differential diagnosis of any patient with unexplained fever, especially when no other cause for the fever can be elucidated, sometimes after antimicrobial therapy has already been started⁽⁶⁻⁸⁾. The recognition of drug fever is clinically important because, if drug fever is not recognized diagnostically, patients may require prolonged hospitalization, unnecessary medications, and potentially harmful diagnostic or therapeutic interventions^(5,9). Drug fever has resulted in life-threatening events (0.6%), hospitalization or prolonged hospital stay (24.5%), and persistent disability (0.6%). A favorable final outcome occurred in 96.9% of cases after drug discontinuation⁽¹⁰⁾.

Drug administration can upset the body's normal balance and cause a fever. The drug may interfere with thermoregulation, increase the rate of metabolism,

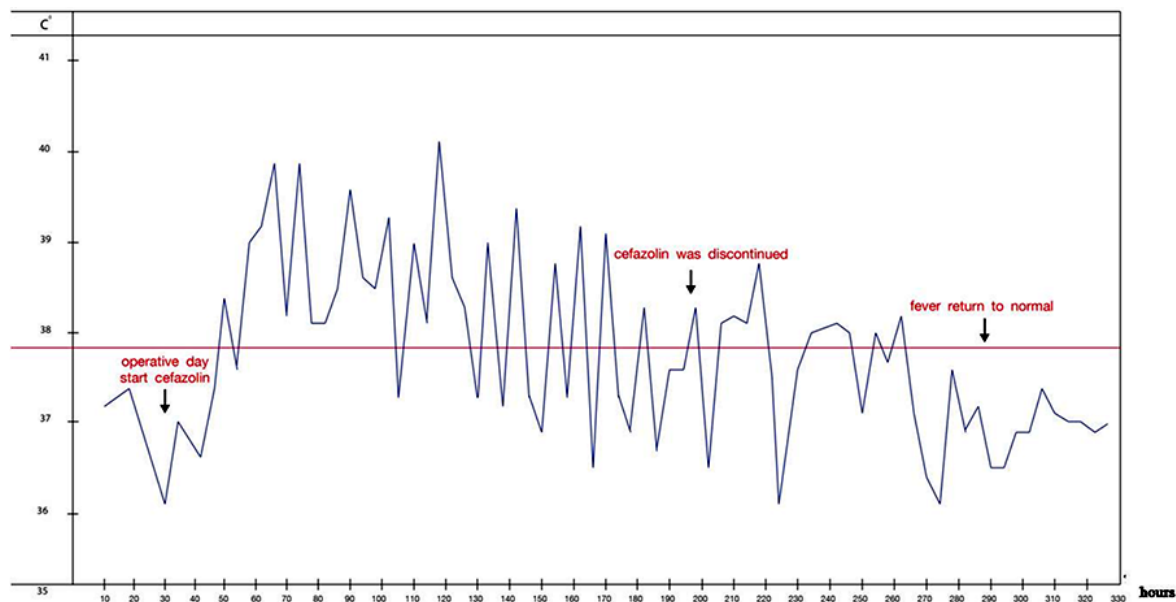


Fig. 1 Changes in patient temperature during the postoperative period.

evoke a cellular or humoral immune response, mimic endogenous pyrogen, or damage tissues. The most common mechanism is probably an immunologic hypersensitivity reaction mediated by drug-induced antibodies⁽⁹⁾ and its characteristics resemble those of an allergic reaction⁽¹¹⁾.

Many factors may indicate the likelihood of a drug-related fever. Males and the elderly appear more prone to this condition. However, no apparent associations of drug fever with systemic lupus erythematosus, atopy, female sex, or advanced age were found⁽¹²⁾. Vodovar et al reported that antibacterials represented the most frequently reported drugs (including amikacin, oxacillin, cefotaxime, ceftriaxone, rifampicin, vancomycin, ciprofloxacin, isoniazid, and cotrimoxazole) and that median time from drug administration to fever onset was 2 days (1.0-10.5 days). The median time for the diagnosis of drug fever following cessation of the suspected drugs was 3 days (1.0-11.5 days) after fever onset⁽¹⁰⁾. Oizumi et al reported that beta-lactams most frequently induced drug fever, including piperacillin (17%), cefotaxime (15%), ceftizoxime (14%), and cefoperazone (8%). In contrast, the incidence of drug fever caused by ampicillin and cefazolin were 3% and 0%, respectively⁽¹³⁾.

Drug fever has no characteristic fever pattern with a highly variable lag time between the initiation of the offending agent and the onset of fever and an infrequent association with either rash or eosinophilia⁽¹²⁾. In non-sensitized individuals receiving a drug for the first time, the onset of fever is highly variable and differs among drug classes. However, fever typically occurs seven to ten days after treatment and usually resolves within 48 hours of discontinuing the administration. Moreover, fever will rapidly reappear if the drug is restarted^(7,9,11).

The common clinical manifestations of drug-induced fever, especially antibiotic, are low-grade fever with early onset followed by remittent high-grade fever. The highest diurnal body temperature rises gradually, and then subsides abruptly after discontinuance of the causative drug. This pattern of fever was found in about 70% of the cases resulting in drug fever. Transient serum lactic dehydrogenase elevation was associated with drug fever in about 51% of cases. Additionally, the transient decrease of platelets and neutrophil counts was found in 8% and 23% retrospectively of drug fever cases⁽¹⁴⁾. Re-challenge will frequently cause recurrence of fever within a few hours and that may be used to confirm the diagnosis. However, re-challenge is controversial and should be undertaken with a high

degree of caution, because there is the potential of a more severe drug reaction⁽⁷⁻⁹⁾.

In the present case, the diagnosis of drug fever was delayed because the onset of fever appeared immediately after the operation, which was highly unusual, and the presence of allergic cutaneous manifestations were not observed. The routine investigations that were performed for purposes of determining the causes of the postoperative fever included urinalysis, chest radiography, blood and urine cultures, duplex scan for deep vein thrombosis, and tip of drain culture. The results of these investigations were negative, so drug fever was suspected. Seventy-two hours after discontinuation of cefazolin, the patient's temperature returned to normal. Drug re-challenge was not performed after discussing the risks and benefits with the patient. Prompt identification of drug-related fever can obviate unnecessary diagnostic procedures and inappropriate treatments^(15,16).

Conclusion

The present case study profiling a 58 year-old woman presenting with progressive back pain and neurogenic claudication. The patient developed a postoperative drug fever that was caused by prophylactic cefazolin. Cefazolin was not initially suspected and this caused a delayed diagnosis because the fever appeared immediately after surgery. Drug fever is usually diagnosed by exclusion after the elimination of other potential causes. The authors would like to encourage physicians to be aware of this entity.

What is already known on this topic?

Previous studies have revealed that drug fever from cefazolin is a rare condition. Most of the known antibiotic-related fever causes are penicillin and cephalosporins, excluding cefazolin. Most of the cases had median onset from drug administration to fever and the median time that it took for patient temperature to return to normal after cessation of the suspected drugs ranged from 1-10 days.

What this study add?

The profiled case shows that drug fever from cefazolin may be a possible cause of immediate postoperative fever. Cefazolin as a possible cause may delay fever management due to the necessity having to rule out other possible causes of fever. The research authors would like to encourage physicians to be aware of this entity, especially in postoperative fever that has unknown causes.

Potential conflicts of interest

None.

References

1. Garibaldi RA, Brodine S, Matsumiya S, Coleman M. Evidence for the non-infectious etiology of early postoperative fever. *Infect Control* 1985; 6: 273-7.
2. Galicier C, Richet H. A prospective study of postoperative fever in a general surgery department. *Infect Control* 1985; 6: 487-90.
3. Livelli FD Jr, Johnson RA, McEnany MT, Sherman E, Newell J, Block PC, et al. Unexplained in-hospital fever following cardiac surgery. Natural history, relationship to postpericardiotomy syndrome, and a prospective study of therapy with indomethacin versus placebo. *Circulation* 1978; 57: 968-75.
4. Homrighausen JK, Lazow SK, Berger JR. Drug-related fever due to cephazolin: a case report. *J Oral Maxillofac Surg* 1999; 57: 1141-3.
5. Johnson DH, Cunha BA. Drug fever. *Infect Dis Clin North Am* 1996; 10: 85-91.
6. Hanson MA. Drug fever. Remember to consider it in diagnosis. *Postgrad Med* 1991; 89: 167-70, 173.
7. Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy* 2010; 30: 57-69.
8. Redon J, Pascual JM, Michavila J, Belda A. Drug fever. *Ann Intern Med* 1987; 107: 264.
9. Park HB, Choi JS, Park SH, Kee WJ, Koh YI. Drug fever due to piperacillin/tazobactam loaded into bone cement. *J Korean Med Sci* 2011; 26: 301-3.
10. Vodovar D, LeBeller C, Megarbane B, Lillo-Le-Louet A, Hanslik T. Drug Fever: a descriptive cohort study from the French national pharmacovigilance database. *Drug Saf* 2012; 35: 759-67.
11. Tabor PA. Drug-induced fever. *Drug Intell Clin Pharm* 1986; 20: 413-20.
12. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med* 1987; 106: 728-33.
13. Oizumi K, Onuma K, Watanabe A, Motomiya M. Clinical study of drug fever induced by parenteral administration of antibiotics. *Tohoku J Exp Med* 1989; 159: 45-56.
14. Gore C, David TJ. Drug-induced fever and bone marrow suppression in a 12-year-old girl with cystic fibrosis. *J R Soc Med* 2001; 94 (Suppl 40): 35-7.
15. Lipsky BA, Hirschmann JV. Drug fever. *JAMA* 1981; 245: 851-4.
16. Linares T, Fernandez A, Soto MT, Escudero E, Gacias L. Drug fever caused by piperacillin-tazobactam. *J Investig Allergol Clin Immunol* 2011; 21: 250-1.

การวินิจฉัยไข้ซึ่งเกิดจากยาเซฟาโซลินในผู้ป่วยหนึ่งรายภายหลังการผ่าตัดกระดูกสันหลังบริเวณเอว

ศิริชัย วิชาศรีสมิ, พินพิไล จุฑะสมพากร, ปัญญา ลักษณะพฤษา

ภูมิหลัง: มีรายงานเกี่ยวกับที่เกิดจากยาปฏิชีวนะหลายประเภทโดยเฉพาะกลุ่มเบต้าแลคแตม รายงานผู้ป่วยฉบับนี้รายงานผู้ป่วยชาวไทยที่เกิดไข้หลังการผ่าตัดกระดูกสันหลังซึ่งเกิดจากการได้รับยาเซฟาโซลิน

รายงานผู้ป่วย: ผู้ป่วยหญิงอายุ 58 ปี มีอาการปวดหลัง ร้าวลงขาทั้งสองข้าง ภาพคลื่นแม่เหล็กไฟฟ้ากระดูกสันหลัง ส่วนเอวพบมีการตีบแคบของโพรงรากประสาทและการกดทับเส้นประสาทบริเวณเอวที่ 4 ไปจนถึงก้นกบ ภายหลังการผ่าตัดกระดูกสันหลังและใส่โลหะตามยึดผู้ป่วยมีไข้หลังผ่าตัดโดยไม่พบสาเหตุที่ชัดเจน การเพาะเชื้อจากเลือดรวมและปลายสายระบายไม่พบเชื้อ ภายหลังการหยุดให้ยาเซฟาโซลินเมื่อหลังผ่าตัดวันที่ 5 พบว่าไข้ลดลงจนเป็นปกติหลังผ่าตัดวันที่ 9

สรุป: การวินิจฉัยสาเหตุของภาวะไข้หลังผ่าตัดซึ่งเกิดจากการให้ยาเซฟาโซลินเพื่อป้องกันการติดเชื้ออาจทำได้ลำบาก เนื่องจากต้องทำการคัดแยกสาเหตุอื่นที่ทำให้เกิดไข่ออกให้หมดเสียก่อน จึงแนะนำให้แพทย์ผู้รักษาคำวินิจฉัยสาเหตุนี้ร่วมด้วยในกรณีที่ไม่พบสาเหตุอื่นชัดเจน ซึ่งจะช่วยให้ผู้ป่วยได้รับการส่งตรวจรวมถึงการรักษาที่ไม่จำเป็น
