CASE REPORT
Immunology, Allergic Disorders & Rheumatology

JKMS

DOI: 10.3346/jkms.2011.26.2.301 • J Korean Med Sci 2011; 26: 301-303

Drug Fever Due to Piperacillin/Tazobactam Loaded into Bone Cement

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Received: 21 July 2010
Accepted: 27 September 2010

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This study was supported by a research grant (09182pharmacovigilance889-2116) from the National Institute of Food and Drug Safety Evaluation.

Although drug fever may develop after administration of the drug by various routes, it has not been reported with antibiotic-loaded bone cement. Here, a case of drug fever induced by piperacillin/tazobactam loaded into bone cement is reported. A 72-yr-old woman presented with fever that developed two weeks after insertion of bone cement loaded with antibiotics including piperacillin/tazobactam into the knee joint for infectious arthritis. The fever was associated with a skin rash and blood eosinophilia. The work-up of the fever excluded several causes. Drug provocation test demonstrated that the piperacillin/tazobactam, which had been loaded in the bone cement, was the cause of the fever. The findings of this case suggest that drug fever can be induced by any drug placed and released continuously within the body. Therefore, the evaluation for possible drug fever should include all drugs the patient has been exposed to regardless of the route of administration.

Key Words: Bone Cements; Drug Hypersensitivity; Fever; Piperacillin

INTRODUCTION

Drugs have been estimated to cause 10%-15% of adverse reaction in hospitalized patients in the United States (1, 2). Drug fever occurs in 3%-5% of cases (3). The drug fever is a febrile response that coincides temporally with the administration of a drug and disappears after discontinuation of the offending agent.

Prompt recognition of the drug fever is essential. However, the drug fever is a common condition that is frequently misdiagnosed (1, 3). It is important for clinicians to suspect drugs as a cause of fevers of unknown origin (1). Because clinicians tend to suspect infection as a cause of a patient's fever, the drug fever can lead to overutilization of antibiotics to treat infections that are not present, possibly increasing the risk of adverse drug reaction and the development of resistance to antibiotics (1). In addition, of greater concern is the possibility that the drug fever may become more generalized with resultant tissue damage (4).

The drug fever may develop after administration of the drug by various routes. However, to the best of our knowledge, the drug fever has not been reported with antibiotic-loaded bone cement. Here, a case of drug fever associated with piperacillin/tazobactam loaded into bone cement, which is confirmed by drug provocation test (DPT), is reported.

CASE DESCRIPTION

A 72-yr-old woman with a previous history of left total knee replacement presented to the department of orthopedics with pain and swelling over the left knee joint on May 21, 2009. She underwent knee joint aspirations in local clinic, and was thought to have an infectious knee joint arthritis. She had suffered from diabetes mellitus for three years and had no known drug allergy. Surgery was performed to insert bone cement mixed with the following antibiotics on May 28, 2009: piperacillin/tazobactam (Tazocin®, Wyeth Pharm., Seoul, Korea), ceftezol sodium (Cetrazol®, Sam Jin Pharm., Seoul, Korea), gentamicin (Gentamicin®, Kuk Je Pharm., Seoul, Korea), and vancomycin hydrochloride (Hanomycin®, Sam Jin Pharm., Seoul, Korea). In addition, intravenous ceftezol and vancomycin, as well as oral rifampicin were administered, as shown in Fig. 1.

Two weeks after the insertion of the antibiotic-loaded bone cement, a fever began to develop. Five days later, a maculopapular skin rash developed (Fig. 1). The blood showed an increased eosinophil count (Fig. 1) and C-reactive protein level (11.4 mg/dL). Initially, a thorough history, physical examination, chest radiography, urinalysis, and blood cultures revealed no causes of fever. Further work-up to evaluate the fever was performed. Serological tests for viral infections, including hepatitis A and B,

pISSN 1011-8934
eISSN 1598-6357

Epstein-Barr virus, human immunodeficiency virus, and cytomegalovirus, were all negative. Auto-antibody screening tests were negative for antinuclear and anti-neutrophil-cytoplasmic antibodies. The total immunoglobulin E level was 361 IU/mL. The C3 and C4 levels were within normal range; however, the CH50 had decreased to 17 U/mL. Trans-thoracic echocardiography, computed tomography of the abdomen and chest, and sigmoidoscopy showed no abnormal findings. The etiology of the fever was unknown. Finally, the possibility of a drug fever was considered. Since then, no systemic antibiotics had been administered. However, the fever persisted for two weeks. Body temperature returned to normal one month after the insertion of bone cement (Fig. 1).

The skin prick tests, intradermal tests, and patch tests were negative for the drugs: piperacillin/tazobactam, ceftezol sodium, gentamicin, vancomycin and rifampicin. A single blind DPT was performed with a single administration of therapeutic dose for each drug after written informed consent was obtained. DPTs for ceftezol, gentamicin and rifampicin were negative. However, the DPT for piperacillin/tazobactam was positive; body temperature increased two hours after intravenous administration of piperacillin/tazobactam 2.25 g, and gradually decreased to normal within 72 hr (Fig. 2). No skin rash was accompanied. The DPT to vancomycin showed a reaction consistent with the red man syndrome; however, no reactions were observed during a five hour-slow infusion. Since then, vancomycin has been used with a slow infusion without any adverse reactions for the infectious arthritis.

Finally, our case was confirmed as having drug fever due to piperacillin/tazobactam loaded into bone cement, which was inserted into the knee joint for the infectious arthritis. The patient was recommended to avoid the use the offending antibiotic.

DISCUSSION

In the present case, fever developed two weeks after the insertion of bone cement loaded with antibiotics including piperacillin/tazobactam into the knee joint. The fever was associated with a skin rash and blood eosinophilia. The work-up of the fever excluded several causes. The DPT demonstrated that the piperacillin/tazobactam, which had been loaded in the bone cement, was the cause of the fever. Finally, the present case was diagnosed with drug fever induced by piperacillin/tazobactam loaded into bone cement.

The onset of drug fever is highly variable and differs among drug classes, but most commonly appears after one to two weeks of drug administration (5). Bone cement mixed with antibiotics has been developed to treat local infections of the bone and soft tissue (6). A sustained level of the antibiotic is released to the systemic circulation from the bone cement (7, 8). The bone cement may be assumed to release piperacillin/tazobactam to the

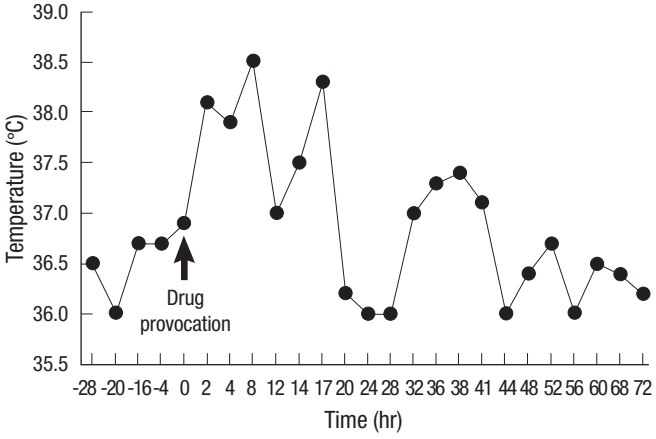

Fig. 2. Drug provocation test with piperacillin/tazobactam.

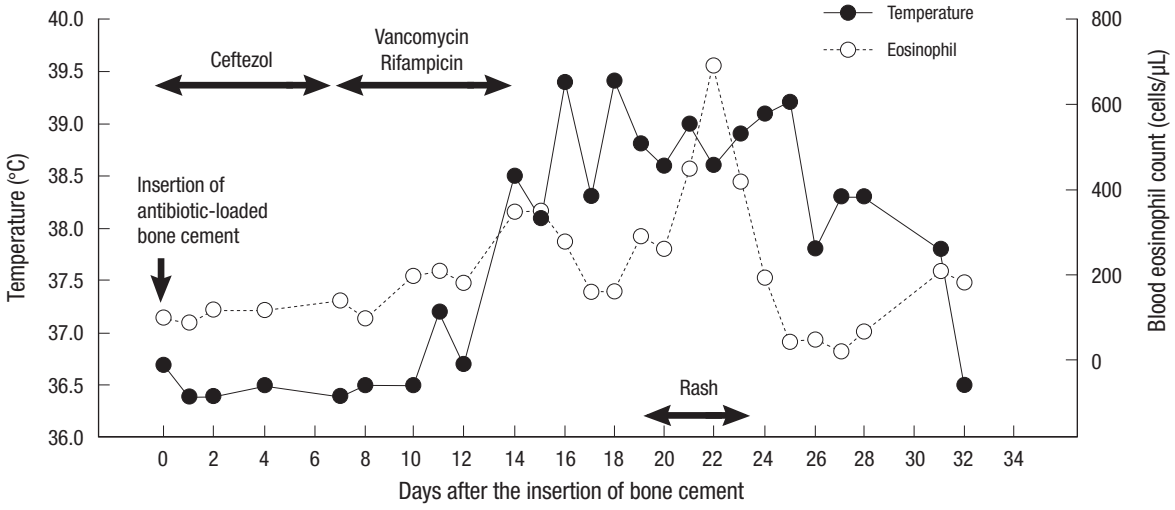

Fig. 1. The development of fever, skin rash and blood eosinophilia in relation to the insertion of antibiotic-loaded bone cement and the administration of systemic antibiotics. The bone cement was loaded with piperacillin/tazobactam, ceftezol sodium, gentamicin and vancomycin hydrochloride.

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systemic circulation at least for two weeks in the present case, based on the observation that the drug fever developed two weeks after the insertion of antibiotic-loaded bone cement. The piperacillin/tazobactam is expected to be continuously released until one month after the insertion of bone cement, on the basis of the finding that the fever disappeared one month after the insertion (Fig. 1). The drug fever usually disappears within 48 to 72 hr after withdrawal of the offending agent (4). Kelm et al. (9) showed that antibiotic-impregnated polymethylmethacrylate hip spacers could inhibit bacterial growth in vitro for 14 to 30 days, suggesting that the antibiotic can be released for at least two weeks.

Our case had evidences to support the diagnosis of drug fever. In drug fever, readministration of the drug produces fever within a matter of hours (4). In the present case, DPT revealed a typical response of drug fever to piperacillin/tazobactam. Fever developed two hours after intravenous administration of piperacillin/tazobactam and gradually decreased to normal within 72 hours. Drug fever is commonly associated with skin rash and blood eosinophilia (4), which were also observed in the present case. The diagnosis of drug fever is one of exclusion after eliminating other potential causes of the febrile reaction; other causes were excluded in the present case. Furthermore, piperacillin is a well known antimicrobial associated with drug fever (5). In the present case, DPT was performed with a single administration of therapeutic dose. However, it may be safer that DPT is performed with graded challenge, which is to administer sufficiently small doses that would not cause a serious reaction initially, and to increase the dose by safe increments (usually 2-fold to 10-fold) over a matter of hours or days until a therapeutic dose is achieved. Generally, the initial starting dose is 1% of the therapeutic dose (4).

The mechanisms associated with drug fever are suggested to be mediated by the formation of circulating antibody-antigen complexes or T-cell lymphocyte immune responses (5). Based on the low serum CH50 levels, the formation of immune complexes with the activation of complement may have been partly involved in the development of the drug fever in the present case.

In conclusion, the findings of this case suggest that drug fever can be induced by any drug placed and released continuously within the body. Therefore, the evaluation for possible drug fever should include all drugs the patient has been exposed to regardless of the route of administration.

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