Case Report

Three-Day Unrecognized Cefazolin Anaphylaxis in a Case Undergoing Coronary Bypass Graft Surgery

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Cephalosporin anaphylaxis is rare but the diagnosis is usually not delayed when the catastrophic reaction occurs shortly after cephalosporin injection. The authors wish to report a patient who had never had a history of beta-lactam hypersensitivity and developed the first episode of cefazolin anaphylaxis during coronary artery bypass surgery. Hypotension developed during the operation but it was immediately corrected by volume infusion and inotrope administration. Shaking chills, drenching sweats, and tingling sensation on the head developed when she regained consciousness from general anesthesia. The adverse reaction disappeared soon and was thought to be the side effects of anesthetic drugs, morphine administrations, and/or blood transfusion. Similar reactions, together with hypotension and oxygen desaturation, recurred each time cefazolin was infused but it took three days and doses of 12 grams of cefazolin administration before a correct diagnosis was reached. The present case report would remind surgeons and anesthesiologists of cefazolin as a potential cause of anaphylaxis during peri- and post-operative periods.

Keywords: *drug allergy, anaphylaxis, type I hypersensitivity, cefazolin, cephalosporins, misdiagnosis*

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Anaphylaxis or type 1 of hypersensitivity to cephalosporin is rare and usually recognized almost immediately if the catastrophic reaction occurs within 30 minutes in whom cephalosporin injection is given without concomitant medication[1-3]. However, when several medications are co-administered in a case with cephalosporin infusion during major surgery, cephalosporin anaphylaxis may escape initial recognition and the reactions were usually thought to be attributed to hypovolemia, septic shock, myocardial failure, or anaphylaxis due to other medications. If cephalosporin anaphylaxis is still unrecognized and cefazolin administration is continued, the anaphylactic reactions could recur several times and lead to unnecessary investigations, and potential lethal outcomes in spite of intensive supportive care. The authors present a clinical scenario of a patient who developed anaphylaxis to intravenous cefazolin and the recognition of cefazolin anaphylaxis was delayed for three days (after 12 grams of cefazolin had been given). The authors wish to raise an awareness of anaphylaxis to cefazolin, which is commonly used for surgical prophylaxis, to surgeons and anesthesiologists, and to highlight the fact that a clinical ground and a high index of suspicion are fundamental to the diagnosis of cefazolin anaphylaxis.

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Case Report

A 62-year-old Thai woman underwent coronary artery bypass graft (CABG) surgery and was given intravenous cefazolin and morphine peri-operatively as an antimicrobial prophylaxis and a pain control regimen, respectively. Mild skin rashes over the forearms were seen shortly after injecting the first few doses of drugs, and it spontaneously subsided. The rash was thought to be related to morphine administration and blood transfusion reaction. During the cardiac bypass graft surgery, hypotension developed and rapid fluid replacement to normalize blood pressure was required. Hematocrit dropped from 36.1% to 27.9% immediately post-operative, which usually occurred after CABG surgery due to blood loss and hemodilution. She was then moved to intensive care unit (ICU) with the continuation of intravenous administration of

cefazolin 1 gm every 6 hours (10-minute infusion) and morphine injection. In the ICU, the vital signs of the conscious-regaining patient were periodically unstable with occasional oxygen desaturation (drop from 97-99% to 85-90%), dyspnea, and palpitation. Morphine injection was discontinued due to a suspicion of narcotics' side effects. Blood transfusion was given and raised final hematocrit to 36.6% within 14 hours in the ICU. Then she was transferred to a private ward where cefazolin was the only drug given intravenously. However, the patient still occasionally experienced frequent episodes of oxygen desaturation, dyspnea, palpitation, and hypotension for the next 10 hours and needed high dose of dobutamine and oxygen supplement to stabilize blood pressure and normalize oxygen saturation. Accordingly, she was transferred back to the ICU due to a suspicion of early cardiac failure.

In the ICU, intensive cardiovascular investigations such as echocardiography, arterial and central venous line catheterization, and monitoring revealed normal intravascular volume and cardiac contractility. Chest roentgenogram revealed bilateral basal pulmonary congestion. Blood chemistries and complete blood counts were within normal ranges. Without suspecting an adverse drug reaction, severe sepsis was the next culprit although a source of infection was still obscure. Hence, intravenous cefepime (1 gram every 8 hours) was initiated, together with the continuation of intravenous cefazolin administration. Although the vital signs were stabilized by several inotropic drugs, she still experienced sporadic dyspnea, chest discomfort, sweating, headache, and blurred vision several times for the next twenty hours and the symptoms each time lasted about an hour. On the third day after the operation, an attending physician noticed that such symptoms of the patient were directly related to the administration of intravenous cephalosporins. Then the diagnosis of drug allergy (immediate type or type 1 of hypersensitivity) to cephalosporin was made and both cephalosporins were immediately discontinued. Thereafter, her clinical deterioration was quickly reverted and she was discharged from the ICU uneventfully. Of note, the patient denied any history of allergic reaction to oral or intravenous cephalosporins. No additional tests, such as skin prick test and serum tryptase level, were performed in this case.

Discussion

The present case definitely developed anaphylaxis manifested by hypotension, oxygen desaturation, chest oppression, shaking chills, sweating and needed inotropic drugs to stabilize her vital signs. Cefazolin was definitely the cause since the reaction followed soon after the infusion and all the adverse reactions disappeared once cefazolin was discontinued. The diagnosis of cephalosporin anaphylaxis in most case reports is immediate[3-7] even in those cases with CABG surgery[5,6]. The presented case is unusual because she survived the anaphylactic reactions from cefazolin infusion 1 gram every 6 hours for a total dosage of 12 grams in three days. The diagnosis of cefazolin anaphylaxis was delayed for three days possibly due to rare report cases of anaphylaxis to cefazolin (28 articles; according to a PubMed search for "anaphylaxis AND cefazolin" in human and English language from 1980-2010) and the prevalence was estimated to be approximately 0.0001-0.1%[8,9]. This cefazolin anaphylaxis can occur without prior cross-reaction to other beta-lactams[10]. Although the anaphylactic reaction is usually overwhelming, the presented case may have developed a milder form of anaphylactic reaction[11] and she received prompt intervention with close monitoring in the intensive care unit. Interesting enough, the severity of the subsequent anaphylactic reactions in response to cefazolin infusions on the second or third day remained similar for the whole three days of delayed diagnosis. Thus, in the present case, cefazolin may not be a good immunogenic stimulant nor elicit strong anaphylactic reaction as she finally survived all of the anaphylactic reactions with full intervention. A review of case reports on cefazolin anaphylaxis revealed many survivors with the immediate diagnosis (Table 1)[2-7,9,10,12-15]. The present case perhaps had the longest duration of delayed diagnosis of cefazolin anaphylaxis and still survived.

In a surgical setting, anaphylactic reactions are often thought by surgeons or anesthesiologists to be due to latex[16], muscle relaxants, hypnotics, opioids, colloids, or other agents rather than cephalosporin, which seems to be very safe in their opinions, especially in a patient without a history of penicillin or cephalosporin allergy. In the present case scenario, the anaphylaxis was firstly attributed to morphine or anesthetic drugs. The subsequent, post-operative reactions were thought to be precipitated by uncorrectable myocardial disease although cardiac surgeon was very confident of the success of the cardiac bypass graft procedure and subsequent investigation of cardiac function showed good cardiac contractility. Septic shock was the last culprit though the source of

Table 1. Summary of case reports of anaphylaxis to cefazolin (with available clinical information)

Authors (year)	Age/sex	Indication for cefazolin administration	History of beta-lactam allergy	Progression	Result
Beaupre et al. (1984)	60/M	AP for aortofemoral bypass graft	No	Intraoperative profound hypotension; immediate recognized by 2-D transesophageal echocardiography	Survive
Konno & Nagase (1995)	-/F	Premature rupture of membrane in pregnancy	n/a	Maternal shock and prolonged fetal bradycardia; required immediate caesarean section	Survive (mother and baby)
Warrington & McPhillips (1996)	19/F	AP for kidney transplantation	No	Immediate hypotension; required vasopressor and a large volume of IV fluid	Survive
	35/F	AP for gallbladder removal	No	Angioedema and wheezing at 5 minute after cefazolin injection; well response to antihistamine	Survive
	23/F	AP for gallbladder removal	No	Wheezing, angioedema, difficulty in breathing and swallowing, and hypotension last 24 hours; treated by epinephrine, antihistamine and steroids	Survive
	29/F	AP for compound tibial fracture	No	Urticaria and severe bronchospasm last 48 hours	Survive
Berrocal & Schuman (2001)	-	Subconjunctiva injection	Yes	Hypotension requiring intensive therapy and airway intubation	Survive
Goodman et al. (2001)	-	AP for orthopedic surgery	Yes	(estimated) One of 300 penicillin-allergic patients had hypersensitivity to cefazolin	-
Gibbs et al. (2003)	34/F	AP for revision of arteriovenous fistula (for hemodialysis)	No	Dyspnea and cardiac arrest at 45 minute after cefazolin injection; required prolonged (2.5 hr) cardiopulmonary resuscitation	Survive
Lee & Castells (2004)	-	AP for surgery	No	Anaphylaxis to cefazolin (determined through postoperative skin testing)	Survive
Jao et al. (2006)	-/F	AP for perinatal group B streptococci infection in pregnancy	No	Required emergency caesarean section	Survive (mother and baby)
Culp et al. (2007)	44/M	AP for c-spine surgery	n/a	Immediate hypotension, bronchospasm, and generalized erythema	Survive
Tayman et al. (2008)	5 months/F	Urinary tract infection	No	Tachypnea and hypotension; good response to pharmacological therapy	Survive
Weissgerber (2008)	79/M	AP for coronary artery bypass graft	No	Hypotension refractory to vasoactive agent and volume repletion; good response to methylene blue	Survive

AP = antimicrobial prophylaxis; n/a = not available

Table 1. (cont.)

Authors (year)	Age/sex	Indication for cefazolin administration	History of beta-lactam allergy	Progression	Result
Carson & Cook (2009)	34/M	AP during hemodialysis in SLE patient	No	Pruritus and shortness of breath shortly after cefazolin injection; expired in next hour	Dead

AP = antimicrobial prophylaxis; n/a = not available

infection was not apparent. Thus, the authors felt compelled to report the peri- and post-operative periods of cefazolin anaphylaxis in the present case, which is challenging in terms of diagnosis, especially in those without any history of beta-lactam hypersensitivity, who had multiple drug administration and underwent major surgery such as CABG.

With a high index of suspicion, cephalosporin hypersensitivity can be easily diagnosed by carefully reviewing the relation of drugs prescribed, together with thoroughly physical examination and the adverse events. Physicians should be aware of the heterogeneity of clinical presentation of hypersensitivity reactions: from mild to life-threatening symptoms. As long as surgical prophylaxis with cefazolin is mandatory, the cefazolin anaphylaxis will certainly recur in other cases but the authors wish its occurrence deserves immediate recognition and proper intervention. The three-day delayed diagnosis in the present case should remind physicians again of the anaphylaxis due to cephalosporin especially when hypotension, chest oppression, wheezing or oxygen desaturation happen during a complicated surgical procedure such as coronary bypass graft surgery. To avoid the unfavorable outcomes of cephalosporin administration, antimicrobial prophylaxis in surgery should limit to one or two doses. If cefazolin hypersensitivity is suspected, it can be substituted by non-beta lactam antibiotics such as clindamycin, or by ceftriaxone (which has a longer half-life and could be more suitable for long duration of surgery). Notably, there has been evidence that the cross reactivity of immediate allergic reaction between cefazolin and ceftriaxone is almost negligible[17,18].

In conclusion, when hypotension, wheezing or oxygen desaturation develop soon after cephalosporin injection whether or not with other medications during major operations, always add cephalosporin anaphylaxis into the list of initial differential diagnosis. Although the severity of cefazolin anaphylaxis may not be life-threatening in some cases, the next victim may not be fortunate to survive several anaphylactic reactions for three days like the present case report.

Potential conflicts of interest

None.

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การวินิจฉัยการแพ้ยาเซฟาโซลินแบบเฉียบพลันล่าช้าถึง 3 วัน ในผู้ป่วยหนึ่งรายที่เข้ารับการผ่าตัดใหญ่แก้ไขหลอดเลือดหัวใจตีบ

วรุตม์ โล่ห์สิริวัฒน์, สมชาย ศรียศชาติ, มานี รักษาเกียรติศักดิ์, อมร ลีลารัศมี

การแพ้ยาเซฟาโซลิน (cefazolin anaphylaxis) เป็นภาวะที่พบได้ยากและมักวินิจฉัยได้ทันที เมื่ออาการผิดปกติเกิดขึ้นทันทีหลังการฉีดยา ผู้นิพนธ์ได้รายงานผู้ป่วยหนึ่งรายที่ไม่เคยมีประวัติการแพ้ยาในกลุ่ม beta-lactam มาก่อน และเกิดการแพ้ยาเซฟาโซลินแบบฉับพลันขณะที่เข้ารับการผ่าตัดใหญ่แก้ไขหลอดเลือดหัวใจตีบ ผู้ป่วยมีแรงดันเลือดตกต่ำขณะผ่าตัดแต่แก้ไขได้ด้วยการให้สารน้ำและยา inotrope ผู้ป่วยรู้สึกหนาวสั่น เหงื่อออก และรู้สึกคันยุกยิกที่ศีรษะเมื่อฟื้นคืนสติจากยาสลบหลังการผ่าตัด อาการไม่พึงประสงค์ดังกล่าวหายในเวลาต่อมา และคิดว่าเกิดจากการให้ยาสลบขณะผ่าตัด ยามอร์ฟีน และ/หรือ การให้เลือด ปฏิกิริยาดังกล่าวเกิดขึ้นอีกพร้อมกับแรงดันเลือดต่ำและความอิ่มตัวของออกซิเจนในเลือดแดงลดลงหลังผู้ป่วยได้รับการฉีดเซฟาโซลิน แต่ใช้เวลาถึง 3 วันหลังจากได้ยาเซฟาโซลินทั้งหมด 12 กรัม กว่าจะวินิจฉัยสาเหตุได้ถูกต้องว่า เกิดจากการแพ้เซฟาโซลิน การรายงานผู้ป่วยรายนี้ เพื่อให้ศัลยแพทย์และวิสัญญีแพทย์ นึกถึงภาวะแพ้ยาเซฟาโซลินแบบฉับพลันไว้ด้วย เมื่อพบผู้ป่วยที่มีแรงดันเลือดต่ำ ใจสั่น เหนื่อย หนาวสั่น เหงื่อออก และความอิ่มตัวของออกซิเจนในเลือดแดงต่ำ ในขณะหรือหลังการผ่าตัดใหญ่