CASE REPORT

IMIPENEM THERAPY FOR SEPTICEMIC MELIOIDOSIS IN A CHILD WITH PENICILLIN AND CEPHALOSPORIN ADVERSE REACTION

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Abstract. The recommended treatment for severe melioidosis is ceftazidime or a combination of ceftazidime and trimethoprim-sulfamethoxazole (TMP/SMX). Amoxicillin-clavulanate has been shown to be an effective alternative therapy. In patient who is allergic to penicillin and cephalosporin, imipenem an alternative drug may be used. We described a 10 year-old boy who was diagnosed as septicemic melioidosis and type 1 diabetes mellitus. He developed fever and rash while being given ceftazidime and TMP/SMX. The fever recurred when amoxicillin-clavulanate was administered orally. He was successfully treated with imipenem.

Melioidosis is an infection caused by *Burkholderia pseudomallei*, a free living organism in soil and water in endemic area (Leelarasamee and Bovornkitti, 1989).The septicemic form of melioidosis has a high mortality . Two randomized trials conducted in Thailand showed that ceftazidime or combination of ceftazidime and trimethoprim-sulfamethoxazole (TMP/SMX) treatment of severe melioidosis were associated with a 50% lower overall mortality compared to conventional treatment (White *et al*, 1989; Sookpranee *et al*, 1992). Amoxicillin-clavulanate has been shown to be an effective alternative therapy (Suputtamongkol *et al*,1994). In a patient who is allergic to penicillin and cephalosporin, imipenem may be used as an alternative drug because of its excellent *in vitro* activity against *B. pseudomallei* (Sookpranee *et al*, 1991), although cross-hypersensitivity between these drugs may occur. This report describes a child with septicemic melioidosis who developed drug fever and rash due to both ceftazidime and amoxicillin-clavulanate and was successfully treated with imipenem.

A previously healthy 10 year-old boy was admitted to our hospital in August, 1991. Two months previously, he was hit by a car and had a bruise on his face. Ten days later, there was a subcutaneous abscess on his chin and he had high grade fever and chill. He was admitted to a provincial hospital. He had increasing dypsnea, pain in his right thigh and another abscess on his forehead. There were echymoses and petechial rashes on the skin. X-ray studies revealed bilateral bronchopneumonia and periosteal reaction of the right femur. Ultrasonographic study of the abdomen revealed no abscess in the liver or spleen.The blood and pus from the abscess grew *B. pseudomallei*. Indirect hemagglutination inhibition antibody (IHA) titer for *B. pseudomallei* was 1:640.The boy was treated with ceftazidime 1 g every 6 hours and intravenous amoxicillin-clavulanate. He was also found to have type 1 diabetes and was treated with regular insulin 3 units 4 times a day. After 21 days of treatment, he still had high fever, abdominal pain and the x-ray of the chest showed progression of pulmonary infiltration, so he was referred to our hospital. Admission examination revealed a cachectic, febrile boy. The temperature was 39ºC, pulse rate 135/minute, respiratory rate 56/minute, blood pressure 100/60 mmHg and his body weight was 19 kg. He was pale. There were multiple old scars representing post surgical drainage of abscesses on his left forehead, right chin, right thigh and right leg. There was an abscess of 3 cm diameter which was fluctuant and inflamed in the right arm. There were fine crepitations in both lungs. The abdomen was slightly distended but there was no hepatosplenomegaly.

Laboratory studies revealed a hematocrit of 25% and white blood cell count 16,900cells/ mm^3 with 80% polymorphonuclear cells, 17% lymphocytes, 3% mononuclear cells, platelet 280,000 cells/ mm^3. Urine examination revealed a specific gravity of 1.019, pH 7.5, albumin 3+, others were negative. The erythrocyte sedimentation rate was 54mm/hour. The chest radiograph revealed reticulonodular infiltration of both lungs, the skull and right thigh radiographs revealed no osteomyelitis. The patient

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was treated with ceftazidime 100 mg/kg/day every 6 hours and intravenous TMP/SMX 10 mg/kg/day every 12 hours. Pus aspirated from the left arm grew *B. pseudomallei* which was susceptible to chloramphenicol, TMP/SMX, doxycycline, ceftazidime, imipenem and amoxicillin-clavulanate by the standard disk diffusion test. The IHA titer for *B. pseudomallei* was 1:2,560. On hospital day 8, rash developed on his face and fever was spiking with maximum temperature of 39ºC. On Hospital day 11, ceftazidime was discontinued and intravenous doxycycline was administered. Fever started to fall 2 days later, but on Hospital day 20, fever began to spike up to 40ºC and rash developed again so doxycycline and TMP/SMX were discontinued on hospital day 22 and imipenem 100 mg/kg/day every 6 hours was started. Fever subsided in 3 days. On hospital day 28, the condition of the patient was improved, oral amoxicillin-clavulanate was given and imipenem was discontinued. The patient again developed high spiking fever with maximum temperature of 40.6ºC but his general condition was good. On hospital day 34, amoxicillin-clavulanate was stopped and imipenem was reinstituted. Fever subsided in 2 days. Imipenem was given for another 12 days then oral doxycycline 100 mg once daily was given as maintenance therapy for 2 months. The total duration of antibiotic treatment was 4 months. At his last follow-up on January, 1992, he was well with a body weight of 23.7 kg. Unfortunately, 3 months later, he died in a car accident.

This boy represented a typical case of disseminated septicemic melioidosis involving multiple subcutaneous abscesses, osteomyelitis and rapidly progressive pneumonia. He was also found to be diabetic which is one of the important underlying conditions associated with melioidosis (Leelarasamee and Bovornkitti, 1989). *B. pseudomallei* infections are very difficult to eradicate and the clinical response may be very slow. In one study, the median time to defervescence after appropriate antibiotic treatment in severe melioidosis patients was 10 days and the organism remained culture-positive from the infected sites for up to 59 days (Suputtamongkol *et al*, 1994). This patient was still febrile and *B. pseudomallei* was recovered from the abscess despite 21 days of antibiotic treatment, however, the organism was still susceptible to the antibiotics previously given.

The maculopapular rash and fever that developed and recurred several times during the course of antibiotic treatment in this patient were most likely due to adverse reactions of ceftazidime and amoxicillin-clavulanate. This was supported by the rapid lysis of fever and gradual disappearance of the rash after discontinuation of the offending drugs (Johnson and Cunha, 1996). The fever and rash that occurred while the patient was given TMP/SMX and doxycycline might be due to enhanced host response to any drug in penicillin-sensitive patients or due to adverse reaction of TMP/SMX. Doxycycline infrequently causes drug fever and rash. Imipenem, the alternative antibiotic for acute treatment of severe melioidosis, was administered to this patient with caution of possible cross-hypersensitivity to penicillin and cephalosporin. He was treated successfully without any adverse reaction. An open, randomized trial conducted in Thailand showed that imipenem and ceftazidime were both efficacious in the treatment of acute severe melioidosis (Simpson *et al*, 1999). However, imipenem is very expensive, so it cannot be recommended as first line antibiotic treatment for severe melioidosis. Imipenem should be reserved for therapy of severe melioidosis in patient who develops adverse reactions to ceftazidime or amoxicillin-clavulanate.

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