

지역사회 획득성 폐렴 및 중증 패혈증이 있는 한 환자에게 Linezolid, Moxifloxacin과 Aztreonam을 초회 정맥 주사 후 ALT/AST 수치의 큰 폭 증가 증례 보고

윤현옥 · Babatunde Osun*

미국 하워드 대학교 약학대학

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Drastic Growth of ALT/AST Level after First Doses of Intravenous Injection of Linezolid, Moxifloxacin and Aztreonam for a Patient with Community Acquired Pneumonia & Severe Sepsis: A Case Report

Hyonok Yoon and Babatunde Osun*

College of pharmacy, Howard University
2300 Fourth Street, N.W., Washington D.C. 20059, U.S.A

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이 증례는 알코올 중독증을 앓은 병력을 가졌으나 간 기능에 특이한 증후가 없던 환자가, 지역 사회 획득성 폐렴으로부터 유발된 중증 패혈증 치료를 받기 위해서 linezolid, moxifloxacin 과 함께 aztreonam을 초회 정맥주사 맞은 후, 아주 높은 수치의 alanine aminotransferase (ALT), aspartate aminotransferase (AST) 혈중 농도가 검출된 경우이다. 후속 치료에서 상기 3가지 항생제 대신 vancomycin과 ceftazidime을 주사했더니, ALT/AST가 빠르게 정상화됨이 관찰되었다. 이 증례 보고는 linezolid, moxifloxacin과 aztreonam을 함께 사용할 경우, 각별한 주의 관찰이 필요하며, 알코올 중독증을 앓은 병력을 가진 환자에게 투여 시 특별한 주의와 함께 AST/ALT혈중 수치를 검사토록 권하기 위한 것이다.

□ Key words - ALT, AST, Linezolid, Moxifloxacin, Aztreonam

Linezolid, one of the fluorinated oxazolidinone class of drugs, has useful activity against most gram-positive organisms including *Staphylococcus aureus* or *Staphylococcus pneumoniae*, vancomycin-resistant enterococcus and methicillin-resistant *Staphylococcus aureus* (MRSA)^{1, 2)} as a protein synthesis inhibitor.³⁾ Linezolid has been known to cause common side effects like diarrhea, headache, nausea and vomiting. The increased ALT (2% to 10%) AST (2% to 5%) alkaline phosphatase (<1% to 4%) thrombocytopenia (about 2%) were also documented.⁴⁾ It is also known as a safe drug to be used for patients of all ages or persons with poor

hepatic and renal function.⁵⁾

Moxifloxacin, a fourth-generation synthetic fluoroquinolone antibacterial agent, functions by inhibiting bacterial DNA gyrase and topoisomerase IV.^{6, 7)} It is effective against broad spectrum of bacteria. It can be administered to cure a number of infections including respiratory tract infections, cellulitis, anthrax, intraabdominal infections, endocarditis, meningitis, and tuberculosis⁷⁻¹⁰⁾ The most frequently reported adverse events in moxifloxacin recipients were nausea, diarrhea, dizziness. Moxifloxacin occurs rarely side effects of hepatotoxicity.

Aztreonam is a synthetic monocyclic beta-lactam antibiotic, with the nucleus based on a simpler monobactam isolated from *Chromobacterium violaceum*.^{11,12)} It blocks mucopeptide synthesis in the bacterial cell wall, so disrupting peptidoglycan crosslinking. Aztre-

Correspondence to : Babatunde Osun
Babatunde Osun, College of Pharmacy, Howard University 2300 4th Street, NW, Washington, DC 20059, U.S.A.
Tel: 1-202-806-9076, Fax: 1-202-806-4636
E-mail: Babatunde.Osun@va.gov

onam is strongly active against only susceptible aerobic gram-negative organisms, including *Pseudomonas aeruginosa*. However, aztreonam is inactive against gram-positive and anaerobic organisms due to very rarely binding with penicillin-binding proteins of them.^{13, 14)} Aztreonam is bactericidal but less so than some of the cephalosporins although it is similar in action to penicillin.¹⁵⁻¹⁷⁾ It is widely known that the common adverse effects of aztreonam are rash, nausea, vomiting, diarrhea, pain at the injection site and thrombophlebitis. Hepatitis, jaundice and liver enzymes increased can happen very rarely (<1%) on administration with aztreonam.¹⁸⁾

This article is to report an unusual case that very high levels of alanine amino transferase (ALT) and aspartate amino transferase (AST) were measured when concomitant use of linezolid moxifloxacin and aztreonam were administered to a patient with community acquired pneumonia (CAP) and severe sepsis.

CASE REPORT

The patient was a 54 year old black man in 175.3 cm (5' 9") height 63.8 kg (140lb 10.5oz) weight with allergy of penicillin class. He was admitted to emergency department (ED) with severe sepsis from CAP. His chief complaint was coughing up with blood and weakness for 3 days before the admission.

On the admission day, his heart rate (HR) was 109, pulse was 133, and body temperature was 38.1°C (100.6°F). Also, blood pressure (BP) was 103/53 mmHg and respiratory rate (RR) was 30, SpO₂ 89%. His chest was rales/rhonchi on the left anterior lung exam and decreased breath sounds on the left anterior lung exam. His intake was 4550 mL/output 0 ml and his net gross was 4550 mL over last 24 hours. In addition, his lab data were white blood counts (WBC) 27.5 red blood counts (RBC) 2.15, platelet (PLT) 52, serum creatinine (SCr) 0.86, blood urea nitrogen (BUN) 7, HCO₃ 20, CL 108, K 3.9, Na 143, hemoglobin (HGB) 7.2, hematocrit (HCT) 23.8, international normalized ratio (INR) 1.7, prothrombin time (PT) 18.2, ALT 34, AST 45 (Table 1). His last drink was 6 days before the admission.

In ED, he was coughing with hypoxia, tachypnea and decreased blood pressure and a large left upper lobe consolidation found on his chest x-ray. He was started on early goal-directed therapy (EGDT) to receive a central venous catheter capable of measuring central venous oxygen saturation Antibiotics with linezolid 600 mg IV, aztreonam 1000 mg IV and moxifloxacin 400 mg IV for CAP once respectively were given. He was intubated for rapid respiratory rate and hypoxia. He was given 3 L normal saline, 1 unit of blood and norepinephrine 0.08 mcg/kg/min for septic shock prior to transferring to the intensive care unit (ICU).

Patient's general appearance was ill appearing and closed eyes, his mental status was alert and confused. He was tachycardia and his abdomen was soft, non tender, no masses or organomegaly. His motor and sensor was grossly normal bilateral condition. No cyanosis or edema, clubbing on his extremities. His alcohol level

Table 1. Lab Data of the patient's vital signs during 1 day before and 2 days after hospital admission

Components	Range(units)	Date of Admission			
		-1	0	1	2
Na	137-145(mEq/L)	145	143	144	146
K	3.5-5.3(mEq/L)	3.8	3.9	4.3	3.8
Cl	98-107(mEq/L)	115	108	114	118
HCO ₃	22-30(mEq/L)	18	20	20	18
BUN	7-17(mg/dL)	7	7	7	5
Mg	1.5 - 2.5 (mg/dL)	1.7	1.8	1.9	2.3
Serum Creatinine	<<1.11(mg/dL)	0.71	0.86	0.76	0.54
Blood Glucose	60-159(mg/dL)	95	94	92	94
Hemoglobin (HGB)	13-17.0(g/dL)	9.3	7.2	9.6	9.7
Hematocrit (HCT)	39.0-51.0(%)	30.6	23.8	32	32.2
Platelets (PLT)	140-400 (K/ μ L)	47	52	60	80
MCV	80-100 (fL)	103	110	103	102
RDW,RBC	11.9-14.3 (%)	29.7	29.8	26.6	24.2
Red Blood Count's(RBC)	4.1-5.7(M/ μ L)	2.09	2.15	3.12	3.57
Lactic Acid	(0.7-1.9 mmol/L)			5.0	3.2
PT			18.2	17.4	
INR			1.7	1.6	
PH			7.32	7.31	
P O ₂				130	
PCO ₂			36	33	
SpO ₂	(%)		89	95	100

PLT's MORPHOLOGY; LARGE

was negative in ED. On chest x-ray, he had obvious left sided pneumonia since he was alcoholic at risk for multiple and atypical infections.

He had the medical history of anemia in 2007, esophagus varices in 2009, schizophrenia, chronic pancreatitis, alcohol abuse and smoking in 2008. He was also a drug user. He was administered with pneumococcal polysaccharide in 2009.

He was taking only acetaminophen 650 mg PO every 6 hours as needed and pantoprazole 20 mg PO once daily only before the admission.

When he was admitted, linezolid 600 mg, moxifloxacin 400 mg and aztreonam 1000 mg were injected and his lab data including AST and ALT were measured. After 6 hours of the injection, his AST was 648, and ALT was 104, which were unusually high level compared to the normal level of AST (5-43 IU/L) and ALT (5-60 IU/L). At the time, his lab data were SCr 0.76, Na 144, K 4.3, HCO₃ 20, CL 114, BUN 7, WBC 15.4, HGB 9.6, HCT 32, PLT 60, HR108, BP 112/68, RR 43, SpO₂ 95%, lactate 5.0 (Table 1). Firstly, hemodialysis was performed followed by being given 2 L of normal saline for 4 hours. Then linezolid, moxifloxacin and aztreonam were switched to ceftazidime 1000 mg every 8 hours and vancomycin 1000 mg every 12 hours IV immediately by an infectious disease's doctor while waiting the results of culture. Ceftazidime was given for covering Gram negative organisms as well as *Pseudomonas aeruginosa*. Vancomycin was injected for Gram positive organisms. Also 100 mL/hour of normal saline were administered to the patient.

After such treatment, his AST/ALT levels had been reduced dramatically after IV fluids and discontinuation of aztreonam, moxifloxacin and linezolid (Figure 1, 2). Lactic acid level also decreased significantly after the above treatment and antibiotics changed (Figure 3).

The WBC of the patient, which was increased abruptly due to severe sepsis with CAP on the admission day, had reduced gradually since antibiotics were started (Figure 4). Body temperatures were fluctuated until 2nd days of admission. Then, they were decreased gradually (Figure 5) and his coughing up blood was

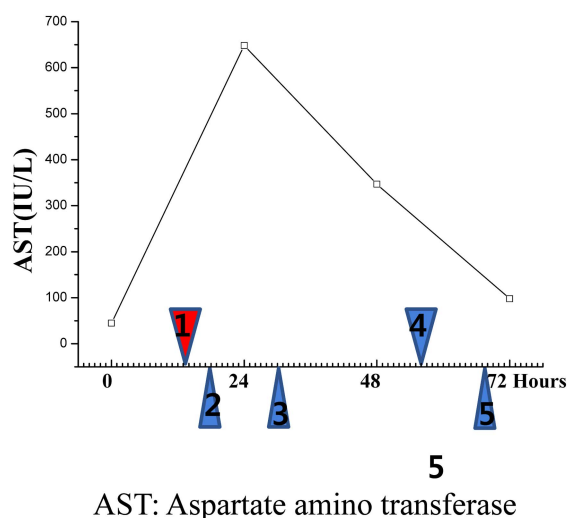


Figure 1. The patient's AST measurement during hospital admission.

- 1: Emergency department admission time in Hospital
- 2: IV injection time of Linezolid 600 mg once, Moxifloxacin 400 mg once, Aztreonam 1000 mg once
- 3: IV injection time of Vancomycin 1000 mg Q 12 hours, Ceftazidime 1000 mg Q 8 hours
- 4: Time got results of blood culture
- 5: IV injection time of Ciprofloxacin 500 mg Q 12 hours instead of Vancomycin

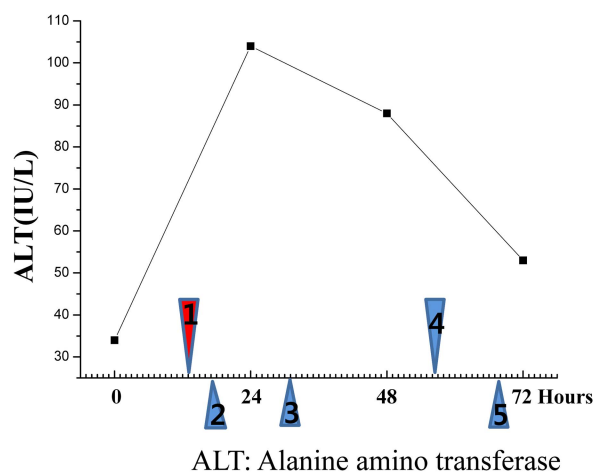


Figure 2. The patient's ALT measurement during hospital admission.

- 1: Emergency department admission time in hospital
- 2: IV injection time of Linezolid 600 mg once, Moxifloxacin 400 mg once, Aztreonam 1000 mg once
- 3: IV injection time of Vancomycin 1000 mg Q 12 hours, Ceftazidime 1000 mg Q 8 hours
- 4: Time got results of blood culture
- 5: IV injection time of Ciprofloxacin 500 mg Q 12 hours instead of Vancomycin

stopped on the 2nd day of the admission.

After *Pseudomonas aureus* showed up on the urine and blood cultures, ciprofloxacin replaced vancomycin to cover pseudomonas organism as the Sanford guideline instructed.

Patient's all physical and lab data were gradually stable and finally he was discharged after 8 days of the admission.

DISCUSSION

This is the first case showing the buildup of AST, ALT and lactic acid after just one time IV injection of combination with linezolid, moxifloxacin and aztreonam.

This case suggests that these adverse effects were caused by several predisposing factors such as concomitant use of linezolid, moxifloxacin and aztreonam, smoking, drinking, drug abuse, or acetaminophen.

There have been reported over 600 drugs bringing about liver disease where the diagnosis of drug-induced liver injury (DILI) is based on marked elevation in liver enzymes or jaundice which cannot be implicated due to any other cause.¹⁹⁾ Also, some researchers have claimed that about 10% mortality of hepatocellular jaundice is associated with drug in U.S.A and the most frequent DILI is caused by antibiotics.²⁰⁾ Some others has reported that most of drug-induced DILI happens within 1 week to 3 months of administration and liver damage present as acute hepatocellular injury, cholestatic injury, granulomatous hepatitis, vascular insult, chronic hepatitis or neoplastic lesion.²¹⁾

It is a very rare report on fatal hepatotoxicity caused by linezolid. A case report was presented about the development of severe liver failure and lactic acidosis after 50 days administration with linezolid; a 55-year-old Caucasian woman was suffered from microvesicular steatosis after long term treatment with linezolid because of infected hip prosthesis. In this case, linezolid toxicity was considered to be the cause of the lactic acidosis and the severe hepatic failure.²²⁾ However, no report was described about the liver dysfunction

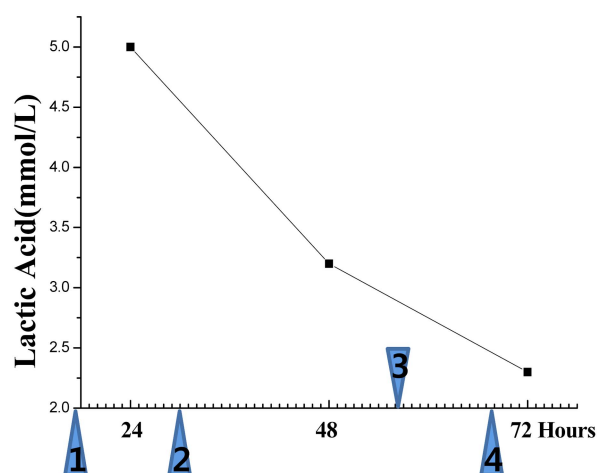


Figure 3. The patient's lactic acid measurement during hospital admission.

- 1:** IV injection time of Linezolid 600 mg once, Moxifloxacin 400 mg once, Aztreonam 1000 mg once
2: IV injection time of Vancomycin 1000 mg Q 12 hours, Ceftazidime 1000 mg Q 8 hours
3: Time got results of blood culture
4: IV injection time of Ciprofloxacin 500 mg Q 12 hours instead of Vancomycin

with only one dose of linezolid.

Fluoroquinolone can induce liver injury rapidly as well as chronically in onset. The pattern of injury can be hepatocellular, cholestatic, or mixed. Mixed cases are the least severe,²³⁾ but the very rare literature on fatal hepatotoxicity caused by moxifloxacin was reported.^{19, 24, 25)} A scant case of fatal hepatotoxicity caused by moxifloxacin was presented in a 72-year-old man.¹⁹⁾ In addition, although moxifloxacin is metabolized mainly in liver via glucuronide and sulfate conjugation, cytochrome P450 system is not involved and thus there are few drug-drug interactions associated with moxifloxacin.⁷⁾

Unlike from the above reports, this case was with the drug interaction among linezolid, aztreonam and moxifloxacin which has not been reported yet. The patient did not have any marked causes to increase ALT/AST and lactic acid. Factors suspected to cause this unexpected reaction were drug interaction, alcohol abuse, current use of acetaminophen or pantoprazole, norepinephrine or synergic adverse effects which may induce liver dysfunction.

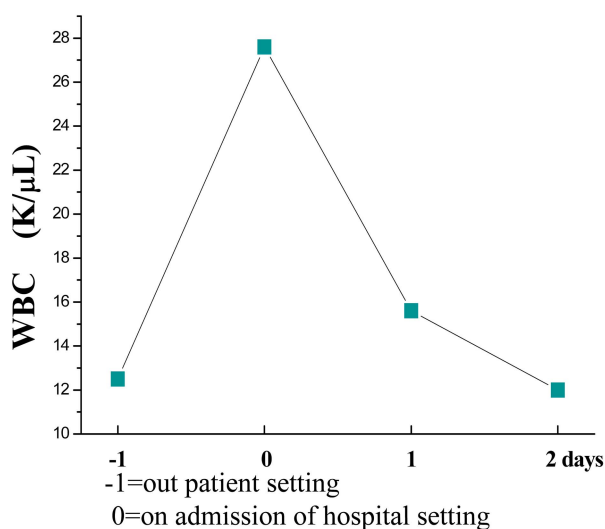


Figure 4. The patient's WBC measurement between 1 day before and the 2nd day after hospital admission.

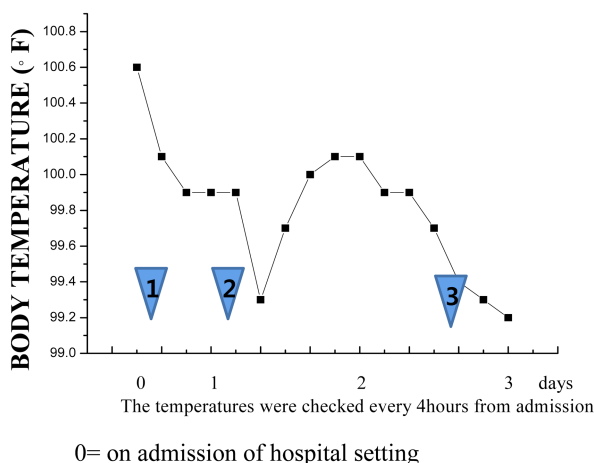


Figure 5. The patient's body temperature measurement between the day and the 3rd day of hospital admission.

1: IV injection time of Linezolid 600 mg once, Moxifloxacin 400 mg once, Aztreonam 1000 mg once

2: IV injection time of Vancomycin 1000 mg Q 12 hours, ceftazidime 1000 mg Q 8 hours

3: IV injection time of Ciprofloxacin 500 mg Q 12 hours instead of Vancomycin

Although alcohol and acetaminophen were potential risk causes for liver problem, these could not be considered as major risk factors to bring about AST/ALT and lactic acid buildup since he drank 6 days before admis-

sion of ED and he had used to get acetaminophen only as needed as well as not exceeded 4000 mg acetaminophen per day. There were no reports so far suspecting drug interaction among linezolid, moxifloxacin, aztreonam, acetaminophen and pantoprazole except possible increased blood pressure due to concomitant use of linezolid and norepinephrine that are contraindicated to use together. The concomitant use of norepinephrine, a direct-acting alpha-/beta-agonists with linezolid, a monoamine oxidase inhibitor (MAOI) therapy should be avoided, concomitant therapy should be carefully monitored for the development of increased blood pressure response if need. In this case, however, the adverse effect caused from the concomitant therapy was minor though the patient's blood pressure was developed slightly from 103/53 mmHg to 112/68 mmHg which was still within normal range (120/80 mmHg).

Another possibility is with the antibiotic effects of linezolid, moxifloxacin and aztreonam respectively. However, they cause liver dysfunction rarely and linezolid may induce lactic acidosis. Being existed some considerable possibilities as the above, it is hard to say that any of them is the major cause of this case. Only high possible case remaining un-neglected is with the synergic adverse reaction of concomitant linezolid, moxifloxacin and aztreonam although each of these drugs had rare side effects of liver dysfunction. Specially, the synergic adverse reaction of the combination might happen to the patient who suffered from alcoholism.

This rare case of the highly elevated ALT/AST and lactic acid due to the concomitant effect of linezolid, moxifloxacin and aztreonam may give alert for health providers to monitor carefully since unexpected synergic adverse reactions could be possible when patients are treated even with drugs which are safe individually.

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