Case Report

Cefazolin induced Seizures in Hemodialysis Patients

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Cephalosporins are epileptogenic drugs, especially when excessive dosages are used or when the drugs are used in patients with decreased renal clearance. The present case report showed that a chronic kidney patient receiving hemodialysis developed generalized tonic clonic seizures when an inappropriate high dose cefazolin was given. Cefazolin 2 g iv q 8 h was given for 25 days continuously to treat fever of unknown origin in a patient who was a severe renal impairment patient. In a severe renal impairment patient, the maintenance dose of cefazolin should be reduced by half and the interval for administration should be extended to 24 h. Even though hemodialysis could remove cefazolin from the blood circulation, in the presented case the very high dose of cefazolin given was far beyond the ability of hemodialysis to clear the drug. The accumulation of cefazolin, therefore, induced three episodes of seizures on days 14, 21 and 25. More precaution should be taken when prescribing medication to a patient with predisposing factors.

Keywords: *Drug induced seizures, Cefazolin, Dosage adjustment in renal impairment*

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Neurotoxic manifestations following antibiotic administration are infrequently encountered under usual conditions. However, antibiotic induced seizures could occur when a patient was in a high risk condition such as an excessive dose of drug being used, decreased renal function, a condition which damaged the blood brain barrier, preexisting CNS diseases, old age and concurrent use of drugs, which were neurotoxic or those that might lower the seizures threshold[1,2]. Beta-lactam antibiotics, especially benzylpenicillin, cefazolin and imipenem/cilastatin, were reported to be neurotoxic which induced convulsion[1,3]. Other drugs associated with seizures included meperidine, tramadol, amphetamine, tricyclic antidepressant, lithium, SSRI, venlafaxine, etc[4].

Case Report

A 29 year old woman was admitted because of subacute fever (~2 wks), dry cough, diarrhea 4 times a day. She was on hemodialysis. Her urine output was only about 150 ml a day. Two years prior to admission, ultrasound showed that she had a small kidney size. Three months prior to admission, ambulatory peritoneal dialysis was given and then was changed to hemodialysis 2 months prior to admission. Seven days prior to admission, she felt pain at the AV shunt area on her left hand and a bruise was observed.

On admission, BT was 38.8 C, BP 176/100 mmHg, PR 78 per min, crepitation at RLL and hepatomegaly were detected. She was moderately pale, her BUN was 60.7 mg%, and serum creatinine was 10.9 mg%. Source of infection could not been identified. Cefazolin 2 g IV q 8 h was given to treat fever of unknown origin. Other medications given were hydralazine, prazocin, atenolol, nifedepine CR, methyldopa, sodamint, folic acid and FBC. Fever went after cefazolin was given but she still received cefazolin continuously for 25 days. On day 14, the patient developed generalized tonic clonic seizures with aura. Neurological exam was performed but no neurological deficit was detected. She, therefore, received no treatment for the seizures apart from intensive observation for any

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neurological disorders. Seven days later, the patient developed another generalized tonic clonic seizure. She was treated with diazepam injection and phenytoin. Four days later, she developed the third episode of generalized tonic clonic seizure. Drug induced seizures was suspected. Cefazolin was thought to be the cause and was discontinued. The patient did not develop any more seizures after cefazolin was discontinued until the patient was discharged 10 days later. She was readmitted 2 months later with hypertensive crisis but no more seizures were seen. Naranjo's algorithm and WHO's algorithm to assess for causality level of drug induced seizures were tested. Both algorithms showed definite or certain level of cefazolin induced seizures.

Discussion

In the present case, the patient was a chronic kidney disease patient with serum creatinine of 10.9 mg%. The administration of 2g IV cefazolin q 8 h was inappropriately high. In a patient with normal renal function, cefazolin is eliminated, unchanged via the kidney, 80-100%[5]. In the present case, after a loading dose, cefazolin maintenance dose should have been reduced by half and the interval for administration should have been extended to 24 h[5]. Although the patient in the presented case was on hemodialysis, which could eliminate cefazolin, hemodialysis could eliminate cefazolin by only 20-50%[5]. Even if plasma concentrations and CFS concentrations of cefazolin were not determined, it was believed to be very high because the drug was administered with inappropriately high dose for a long time in a patient with reduced clearance. Cefazolin would, therefore, accumulate and cross blood brain barrier into the CFS and the brain.

Experimental studies showed that cefazolin interacted with gamma aminobutyric acid (GABA) receptor complex then diminished the neurological inhibitory pathway. Seizure activity may be expressed by the changes of EEG demonstrating diffuse slow sharp wave form in all leads. Then revert to normal after the drug is discontinued and cleared from the CNS[2,6]. Epileptogenic reaction of cephalosporins is correlated with the size of substituent at positions 3 and 7 of 7-cephalosporanic acid structure of cephalosorins. The larger the substituent, the more serious the epileptogenic profile of the drug. Cefazolin has two heterocyclic rings at positions 3 and 7, therefore demonstrated a greater epileptogenic activity[3,7].

Beta lactam antibiotic induced seizures would manifest as myoclonus form originates with ocular twiching then progressing to generalized jerking movements of all muscles[2]. Cefazolin associated seizures have been reported before, which were associated with decreased renal function and intraventricular route[8-10]. In three case reports of Bechtel et al, all the patients were impaired renal patients receiving a high dose of cefazolin for a prolonged period and developed generalized tonic clonic seizures[9]. In the present case report, generalized tonic clonic seizures were observed similar to the previous reports.

Conclusion

Cephalosporins, especially the first generation that has greater epileptogenic activity, could induce seizures particularly when used in a patient having predisposing factors. More attention should be paid to a patient with predisposing factors (old age, high dose, reduced clearance, co-morbid CNS disorders or drug interactions) and appropriate dosage adjustment should be performed in order to minimize the risk of adverse neurological manifestations that may occur.

References

1. Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: predisposing factors and pathogenesis. J Antimicrob Chemother 1991; 27: 405-25.
2. Barrons RW, Murray KM, Richey RM. Populations at risk for penicillin-induced seizures. Ann Pharmacother 1992; 26: 26-9.
3. Chow KM, Hui AC, Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. Eur J Clin Microbiol Infect Dis 2005; 24: 649-53.
4. Wills B, Erickson T. Drug- and toxin-associated seizures. Med Clin North Am 2005; 89: 1297-321.
5. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Drug information handbook. 13th ed. Ohio: Lexicomp; 2005: 273-4.
6. Hantson P, Leonard F, Maloteaux JM, Mahieu P. How epileptogenic are the recent antibiotics? Acta Clin Belg 1999; 54: 80-7.
7. Goldstein MA, Harden CL. Seizures complication of antibacterial treatment. Available from: URL: http://epilepsy.com/page/infection_complications.html (Accessed January 2006)
8. Yost RL, Lee JD, O'Leary JP. Convulsions associated with sodium cefazolin: a case report. Am Surg 1977; 43: 417-20.
9. Bechtel TP, Slaughter RL, Moore TD. Seizures

associated with high cerebrospinal fluid concentrations of cefazolin. Am J Hosp Pharm 1980; 37: 271-3.

10. Martin ES III, Bagwell JT, Bush-Veith S, Renger H Jr. Seizures after intraventricular cefazolin administration. Clin Pharm 1992; 11: 104-5.

การชักจากการใช้ยาเซฟาโซลินในผู้ป่วยที่ล้างไตด้วยเครื่องไตเทียม

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ยากลุ่มเซฟาโลสปอร์รินมีคุณสมบัติที่จะเหนี่ยวนำให้เกิดการชักได้โดยเฉพาะกรณีผู้ป่วยได้รับยาในขนาดสูง หรือ ในกรณีการใช้ในผู้ป่วยที่มีความสามารถในการกำจัดยาได้ลดลง รายงานกรณีผู้ป่วยรายนี้เป็นผู้ป่วยที่ได้รับการล้างไตโดยเครื่องไตเทียมและได้รับเซฟาโซลินขนาดสูงอย่างไม่เหมาะสมจนกระทั่งก่อให้เกิดการชัก ผู้ป่วยรายนี้เป็นผู้ป่วยไตวาย แต่ได้รับเซฟาโซลินในขนาด 2 กรัมทุก 8 ชั่วโมงทางหลอดเลือดดำ นานถึง 25 วัน เพื่อรักษาไข้ที่ไม่ทราบสาเหตุ ในผู้ป่วยไตวายระดับรุนแรงการให้ยาเซฟาโซลินควรลดขนาดยาลงครึ่งหนึ่ง และควรยืดระยะเวลาของการให้ยาออกไปเป็นทุก 24 ชั่วโมง แม้การล้างไตด้วยเครื่องไตเทียมจะสามารถกำจัดยาเซฟาโซลินได้ แต่ในกรณีนี้ผู้ป่วยได้รับยาในขนาดสูงและเป็นเวลานานจนเกิดการสะสมของยาและเหนี่ยวนำให้เกิดการชัก ถึง 3 ครั้ง ในวันที่ 14, 21 และ 25 หลังได้รับยา การใช้ยาในผู้ป่วยที่มีปัจจัยเสี่ยงนั้นจะต้องกระทำด้วยความระมัดระวังมากขึ้นเป็นพิเศษ