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Short Communication

Cefepime induced neurotoxicity associated with kidney injury

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ABSTRACT

Background: Cefepime is a broad-spectrum, 4th-generation, cephalosporin used to treat moderate to severe bacterial infections. Overall displaying a favorable safety profile, potentially life threatening neurologic complications can occur. Objective: To describe a case of cefepime induced neurotoxicity and discuss the clinical features commonly associated with this condition. Case Report: A 52 year-old female undergoing outpatient treatment with cefepime and vancomycin for severe osteomyelitis developed acute alteration of mental status, hallucinations, encephalopathy and myoclonus. Her vancomycin had been stopped due to a rise in serum creatinine; however adjustments in her cefepime dosing were not made. The etiology of her neurologic symptoms were unclear to the emergency physician who initially treated her, however, after a multidisciplinary effort, cefepime toxicity was felt to be explanatory. Summary: Cefepime induced neurotoxicity is generally encountered in the patient with underlying or newly developed renal dysfunction. Failure to adjust cefepime dosing and concurrent use of aminoglycosides are common themes in this condition. Management with hemodialysis has been shown to hasten cefepime elimination, thus prompt consultation with nephrology should be considered. Conclusion: We report a case of cefepime induced neurotoxicity in a 52-year-old female with associated acute kidney injury. This problem is under-recognized in the current emergency medicine literature.

KEYWORDS: cephalosporin antibiotics, neurotoxicity, hemodialysis, myoclonus, renal failure

INTRODUCTION

Cefepime is a broad-spectrum, 4th-generation, cephalosporin used to treat moderate to severe bacterial infection. Overall, it has a favorable safety profile, however potentially life threatening neurologic complications can occur. We report a case of cefepime induced (CIN) neurotoxicity associated acute kidney injury (AKI).

CASE REPORT

A 58-year-old female with type 2 diabetes was presented to the emergency room with acute alteration of mental status. She was on cefepime and vancomycin for a complicated ankle fracture with osteomyelitis. After one month, routine blood work arranged through her primary care physician noted an asymptomatic rise in her creatinine from 1.2 to 2.4 mg/dL.

Concerned by this creatinine rise, the patient's physician ordered the vancomycin to be discontinued. The cefepime dose, however, was not adjusted. Over the next 24 hours the patient developed visual hallucinations, myoclonic jerking, and altered mental status which prompted the patient's husband to bring her to the emergency room.

In the ED, her exam was noted for BP 106/72, HR 72, Temp 36.1, RR 16 and oxygen saturation

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98%. She displaced frequent myoclonus in both her upper and lower extremities. She was not oriented to the date or time, however would follow commands and did not appear distressed or toxic. Extraocular motion was intact without clonus. Pupils were 4 mm and reactive. Her neck was supple. There was a loud systolic murmur, radiating to her right shoulder, but no appreciable rub or gallop. Auscultation of the lungs noted bibasilar crackles. Abdominal exam was unremarkable. A large external fixation device was noted on the right ankle. Skin exam did not demonstrate rash or flushing. Deep tendon reflexes were present and symmetric.

EKG showed a sinus rhythm with an unchanged left anterior fasicular block. T waves were normal. Non-contrast CT of the head was normal. White blood cell count was normal at 10.3 x $10^3/\mu$. Ammonia and thyroid-stimulating hormone were within normal limits. Troponin I was normal. Serum creatinine and potassium had risen to 3.48 mg/dL and 5.7 mmol/L, respectively. Her BUN measurement was 51 mg/dL. Serum sodium, chloride, calcium and bicarbonate were normal. Random vancomycin level was 38.9 µ/mL (vancomycin trough was 30.1 µ/mL the day before [reference range 5-15 µ/mL]). Urinalysis noted 0-2 RBC, 15-20 WBC, protein 100 mg/dL, without casts. Fractional excretion of sodium was 2.9%.

The patient received 30 grams of oral Kayexelate, one ampule of D50, 10 units of regular insulin intravenously for the hyperkalemia. A foley catheter was placed with 250 mL of urine return.

She was admitted to the internal medicine service and neurology, infectious disease, nephrology, toxicology, and orthopedic consultations were obtained. Electroencephalogram noted diffuse background slowly consistent with moderate encephalopathy, however, no epileptiform discharges or evidence of seizure was noted. Nephrology elected not to pursue dialysis initially, however her renal function worsened and serum bicarbonate levels declined which prompted hemodialysis (HD) on hospital day 3.

Within one week of admission, and after her second round of HD, she was back to her baseline mental status with complete resolution of her myoclonus. Cefepime had been discontinued on admission, and the infectious disease team initiated daptomycin and aztreonam for her osteomyelitis. Her renal function never recovered and outpatient dialysis was initiated after hospital discharge.

DISCUSSION

Cefepime is a broad-spectrum, 4th-generation, cephalosporin used to treat moderate to severe bacterial infection. Overall, it has a favorable safety profile. Common adverse effects include headache, nausea and rash [1]. Cefepime, like other betalactam antibiotics, has been associated with neurotoxicity. The common clinical findings with cefepime-induced neurotoxicity (CIN) include encephalopathy and myoclonus. Other features such as coma and non-convulsive status epilepticus (NCSE) have been described as well [2]. Seizure activity is thought to occur by prevention of GABA binding to $GABA_A$ receptors [3].

A common feature, and risk factor for neuro-toxicity, is renal insufficiency. In patients with normal renal function, the half-life of cefepime is approximately 2.3 hours. There is a linear relationship with total body clearance and renal function. That is, as renal function worsens, clearance is reduced. The volume of distribution is 20.5 L/kg [4]. CSF levels are approximately 10% of serum concentration [2]. Good CSF penetration coupled with reduced clearance lends itself to potential neurologic complications.

In case reports, many patients who suffer from cefepime-neurotoxicity are concomitantly on amino glycosides, an independent risk factor for renal injury. Often, adjustments in dosing for decreased GFR have not been made. Additionally, patients who are on other nephrotoxic medication or who are critically ill may develop renal injury and are at risk for neurotoxicity.

In this case, cefepime dosing was not adjusted, and though a cefepime level was not measured (requested by the toxicology service but ultimately not obtained), the finding of myoclonus and encephalopathy is consistent with established cases. While adjusting the dose or discontinuing cefepime prior to the development of neurotoxicity in patients with renal insufficiency may decrease the incidence of neurotoxicity, the standard of care in managing CIN is unclear.

Hemodialysis (HD) is a viable option. Several cases of CIN have been successfully managed with HD [2]. Excluding the common indications for HD (acidosis, volume overload, electrolyte aberrancies, uremia), in relatively stable patients without coma or evidence of NCSE, there are no randomized trials evaluating the efficacy of HD vs. conservative care. HD significantly reduces the half-life of cefepime. Studies utilizing high-flux hemodialysis have shown mean clearance rates of cefepime of 178.9 ml/min at flow rates of 400 ml/min [5]. In patients with various degrees of renal dysfunction, HD reduces cefepime half-life from 13.5 hours to 2.3 hours [4]. Continuous venovenous hemodiafiltration (CVVHD) reduces cefepime half-life as well with mean elimination half-lives in one study of 8.11 hours [6].

CONCLUSIONS

We report a case of cefepime inducted neuro-toxicity associated with acute kidney injury. Hemodialysis has been shown to reduce cefepime half-lives and should be considered in these patients. There is limited information regarding this condition in the current toxicology literature. We feel practitioners who prescribe this medication or treat patients in acute care settings need to have a working understanding of cefepime-induced neurotoxicity.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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