

Myoclonus from antibiotic therapy (Ceftazidime-induced Neurotoxicity): A case study and review

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CASE STUDY

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ABSTRACT

A 78-year-old Chinese man with a history of end stage renal disease (ESRD) presented with fever of one day duration. He was treated for catheter related sepsis with intravenous piperacillin and tazobactam, which was later switched to vancomycin and ceftazidime secondary to persistent fever with negative cultures. On the fifth day of treatment with vancomycin and ceftazidime, he developed new onset upper limb myoclonus which progressed to bilateral upper limb ataxia. A provisional diagnosis of myoclonus and ataxia secondary to neurotoxicity related to ceftazidime was made and the ceftazidime was ceased. His symptoms resolved over three days and he returned to his baseline neurological status by Day 5 following cessation.

Key Words

Myoclonus, ataxia, ceftazidime, neurotoxicity

Implications for Practice:

1. What is known about this subject?

Cephalosporins (including ceftazidime and ceftriaxone) can cause neurotoxicity. This is more common among patients with renal impairment.

2. What new information is offered in this case study?

Myoclonus as a presentation of ceftazidime-induced neurotoxicity in the context of renal impairment, can progress to ataxia without encephalopathy.

3. What are the implications for research, policy, or practice?

The differential diagnosis of ceftazidime or cephalosporin-induced neurotoxicity should be considered with patients presenting with non-localising neurological symptoms, after administration of cephalosporin antibiotics. Early recognition allows discontinuation of the antibiotic and prevents unnecessary or invasive investigations.

Background

Ceftazidime, like other cephalosporins, is a commonly used antibiotic in the hospital setting. However, cephalosporin-induced neurotoxicity is not well recognized, and is likely under-reported especially amongst patients with chronic kidney disease. We present a case of a 78-year-old man who developed myoclonus and ataxia secondary to ceftazidime.

Case details

A 78-year-old Chinese man presented to the emergency department with fever of one day's duration. He had a history of end stage renal disease (ESRD) secondary to hypertensive nephrosclerosis. He was on regular haemodialysis via permanent catheter after the stenosis of his left arteriovenous fistula, and was awaiting fistuloplasty. Comorbidities included dyslipidaemia, diabetes mellitus, antral gastritis and iron deficiency anaemia. He had no localising symptoms for the fever and there was no contact or travel history. Physical examination was unremarkable and he was treated for catheter related sepsis with intravenous piperacillin and tazobactam (2.25g every 6 hourly). However he had persistent fever for one week, and repeated blood and urine cultures yielded no growth of microorganisms. Computed tomography of thorax, abdomen, and pelvis found no source of infection. A transthoracic echocardiogram showed no vegetations. The

infectious diseases team was consulted for pyrexia of unknown origin. Antibiotic therapy was switched to vancomycin and ceftazidime (2g daily with 1g top up after each dialysis, with the intention to treat presumptive melioidosis; an endemic soil-borne disease in South East Asia region). Catheter was removed after fistuloplasty. Culture from tip of the catheter also came back as no growth.

On the fifth day of treatment with the changed antibiotics regime (vancomycin and ceftazidime), he developed new onset of myoclonus of the upper limbs bilaterally. He had no change in mental status suggestive of an encephalopathy. Prior to this he had no such movement disorder or any neurological symptoms. He then progressed to develop bilateral upper limbs ataxia. There were myoclonic movements of the upper limbs. The myoclonic movements were less prominent in the lower limbs. Occasionally there were bilateral hand flaps. There was no apraxia or pseudo-athetosis. No truncal ataxia was observed. Mild right proximal hemiparesis (power 4 over 5 [Medical Research Council Scale, MRC Scale]) was noted when compared with the contralateral limbs.

Magnetic resonance imaging (MRI) of the brain showed no acute intracranial haemorrhage or ischemia. A renal panel was not suggestive of uremic encephalopathy. The ammonia level and liver function tests were within normal limits. A provisional diagnosis of myoclonus and ataxia secondary to neurotoxicity due to the use of ceftazidime on a background of ESRD was made, and the ceftazidime was ceased. The patient's neurological symptoms resolved over 72 hours and he was at his baseline by five days. Electroencephalography (EEG) was scheduled but not done as his symptoms resolved completely.

We searched the literature and noted several publications on neurotoxicity from cephalosporins. Search terms in PubMed were cephalosporin or ceftazidime and neurotoxicity (including myoclonus, seizure, and encephalopathy). The literature search was also extended to the Google search engine and five more case reports obtained. Reports on neurotoxicity from ceftriaxone alone and cefepime alone were not included so that the clinical details were comparable to our patient who received ceftazidime. All case reports that were selected were written in English and involved human subjects. We focused on publications from January 1980 when ceftazidime was first marketed, until March 2017. Clinical details such as demographic data, disease pattern, and EEG findings were obtained. Clinical data of fifteen patients with ceftazidime

induced neurotoxicity from 14 publications were summarised in Table 1.

Discussion

Neurotoxicity effects of ceftazidime were reported in 15 patients from 14 publications, and one patient from our institution. Among these sixteen patients, thirteen had underlying renal impairment (mostly end stage renal disease on renal replacement therapy), two patients' creatinine level was normal, and the remaining one patient's creatinine level was not available.

The median age of all the patients was 64 years old. The indications for treatment requiring ceftazidime among the patients included lower respiratory tract infections/pneumonia (six patients), peritonitis (four patients), and cellulitis, meningitis, malignant otitis media, and preoperative induction. One study found that the cerebrospinal fluid (CSF) permeability for ceftazidime is higher with diseased meninges than in those with normal meninges which could also explained the neurotoxicity described in one patient with meningitis.^{4,15}

EEG findings of eight patients were available.^{3-8,12,13} Seven of them demonstrated epileptic activity including continuous, generalised sharp waves and periodic short interval diffuse discharge (PSIDD), and one showed slow wave which indicated encephalopathy.¹²

Since ceftazidime is not metabolised in the body and is excreted unchanged in active form in the urine by glomerular filtration, patients with renal impairment are more vulnerable to the ceftazidime neurotoxicity even if it is given at recommended doses. Intraperitoneal ceftazidime is the drug of choice in peritonitis and this mode of delivery augments the above observation. One study with intraperitoneal cefuroxime observed increased permeability of the peritoneal membrane during infection which may explain the increased systemic toxicity.¹⁶ The association between neurotoxicity and ceftazidime is not completely understood. In the case reported by Halder et al, the patient had normal renal function and received a single dose of ceftazidime, the episode of generalized seizure was assumed to be attributed to rapid bolus that was infused intravenously.¹⁴

The neurological manifestations from ceftazidime toxicity varied from confusion or hallucinations, to marked signs of myoclonus and seizures. Our patient has progression to ataxia without encephalopathy and this has not been described in published reports. Jackson and Berkovic

suggested that ceftazidime toxicity may lead to disturbance in the deep midline grey matter, causing transient toxic penduncular hallucinosis. The convulsive activity or epileptogenic effect of cephalosporins involves inhibition of gamma-aminobutyric acid (GABA) binding to GABA (A) receptors.¹⁷ The latency in the development of the neurological symptoms ranged from few minutes to fifteen days. The resolution of symptoms typically occurs within two to seven days of discontinuation of ceftazidime. Although outcomes were not available in two case reports, it seems that such neurotoxicity is reversible.

Conclusion

Antibiotic-induced neurotoxicity is often overlooked or misinterpreted despite extensive administration of these agents.⁷ Early recognition of this condition and withdrawal of offending antibiotics is therefore of significant clinical importance. It may prevent unnecessary invasive investigations and serious complications in these already complex renal patients.⁹ Patients presenting with confusion, speech disturbances, temporospatial disorientation and other forms of altered mentation should have an EEG assessment,⁷ as these antibiotics may precipitate seizures even in patients who do not have a predisposition to seizures or known epilepsy. The diagnosis of non-convulsive status epilepticus (NCSE) may be missed if an EEG is not performed.⁸ As the use of ceftazidime and other cephalosporins (especially ceftriaxone and cefepime) is becoming more common, clinicians and physicians ought to have heightened awareness of their potential neurotoxicity in this context.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

The authors, *Ong CY and Qin Y*, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Table 1: Clinical Details of Patients with Ceftazidime Induced Neurotoxicity

Authors	No. of patients	Age/sex	Creatinine (μmol/L)	Dose	Indication	Clinical features	EEG	Latency (days)	Resolution (days)
Zahawi, Sprott, et al. ¹	1	62/F	54.8	IV 2g BD	Chest infection	Auditory and visual hallucination	NA	1	2
Hillsley, Massey ²	1	64/M	218.2	IV 2 g TDS	Cellulitis	Confusion, truncal asterix	NA	15	3
Jackson, Berkovic ³	1	34/M	ESRD	IV 2g BD	Pseudomonas pneumonia	Confusion, generalised myoclonus then GTC seizure	Generalised 3sec spike and wave	3	Immediate with clonazepam
Klion, Kallsen Confusion ⁴	1	77/M	300.6	IV 2 g TDS	Pseudomonas meningitis	Myoclonus of upper limbs, coma	Continuous, generalised, sharp f 2.5Hz discharge	14	2 (with AED)
Martinez, Barriga, et al. ⁵	2	64/M	707.2	IV 2g OM	Pneumonia	Agitation, confusion, myoclonus	Continuous generalised 12Hz sharp wave	8	2 (improved)
		38/M	592.3	IV 2g OM	Pneumonia	Confusion, myoclonus	Continuous, generalised 12Hz sharp wave	5	2 (improved)
Chuang, Chen, et al. ⁶	1	76/F	698.3	IV 2g BD	Pseudomonas wound	Altered consciousness, myoclonus upper limbs	Periodic short interval diffuse discharge (PSIDD)	5	3
Chow, Szeto ⁷	1	62/F	901.7	IP 250mg QID x11days then IV 1g QD x5days	CAPD peritonitis	No verbal response	Increased theta activity triphasic waves	2	NA
Primavera, Cocito, et al. ⁸	1	72 /F	424.3	IV 4g/day	Peritonitis	Mood change, anxiety, mute, extrapyramidal signs, myoclonic jerks	Generalised sharp waves	3	2
Martin ⁹	1	43/M	ESRD	IV 1g daily	Pneumonia	Dysarthria, confusion, no verbal response, facial myoclonic jerks	NA	5	6

S Chan, Turner, et al. ¹⁰	1	65/F	NA	IV 2g BID	Pneumonia	Confusion, asynchronous myoclonus	NA	2	7
Joseph, Vimala ¹¹	1	49/M	ESRD	IV Ig BD	Malignant otitis media	Myoclonus (generalised), Altered sensorium	NA	2	5
Lye, Leong ¹²	1	80/F	595.8	IP 500 mg/L then IP 125mg/L	Pseudomonas peritonitis	Confusion , myoclonus upper limbs	Intermittent bilateral frontal slow waves	10	7
Vannaprasaht, Tawalee, et al. ¹³	1	70/F	ESRD	IV 1g BD then IP 1.5g/day then IP 11g/day x2day	Peritonitis	Altered consciousness, mutism, asterixis, nystagmus	Generalised 3 spikes-and-wave	2	6 (with HD and AED)
Haldar, Kaushar, et al. ¹⁴	1	14/M	Normal	IV 1.5mg STAT	Preoperative induction	Generalised seizures	NA	5	Minutes (with midazolam)