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Original Article

The Safety of Treatment with Cefepime in Elderly Patients

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ABSTRACT

Background/Purpose: Cefepime-induced neurotoxicity has been reported worldwide sporadically. Most patients affected are elderly and have renal impairment. Few cases were identified in our institution and prompted this review to formulate measures to prevent its occurrence.

Methods: This is a quality improvement study done in the Department of Geriatric Medicine, Tan Tock Seng Hospital, Singapore. We retrieved case records of patients who received cefepime between March 2014 and September 2015. Demographic data, comorbidities, indication, duration and doses of cefepime were recorded. Case records of patients which developed neurologic symptoms were independently reviewed. Patients were determined to have cefepime-induced neurotoxicity based on set criteria.

Results: Total of 279 records were reviewed. Cefepime was administered for a mean duration of 3.2 days. Urinary tract infection was the most common indication for prescribing cefepime. Majority of patients were cognitively impaired (n=174, 62%) and had chronic kidney disease (CKD) (n=157, 56%). Six cases (2.2%) were identified to have cefepime-induced neurotoxicity. The mean daily dose of cefepime administered for this group was lower compared to the rest of the cohort, but the duration of treatment was longer. Mean latency period was 3 days and mean recovery period was 4 days. Predominant symptoms were confusion (n=6) and drowsiness (n=5). Other symptoms were myoclonus (n=2) and agitation (n=2). Eighteen patients received higher dose of cefepime based on creatinine clearance, but none of them developed neurologic symptoms.

Conclusion: Since this special group is vulnerable, there should be increased awareness for this condition, diligent adjustment of cefepime dosages according to renal function and timely de-escalation of antibiotics.

1. INTRODUCTION

Cefepime-induced neurotoxicity and encephalopathy have been sporadically reported worldwide. Cefepime is a 4th generation cephalosporin, indicated for moderate to severe infections requiring broad coverage for gram-negative bacteria.

It was reported that around 3% of patients treated with cefepime have experienced adverse central

nervous system effects.[1] Most cases identified have concomitant renal impairment.[2] Frequently they also belong in the geriatric population.[3] The average dose given to those who have cefepime-induced neurotoxicity was 2.5 g/day.[2] Studies have shown that the average latency period from the time cefepime was administered until symptoms was noted to be 5 days.[2,4,5] Recovery period after discontinuing cefepime was 24 to 48 hours.[6]

In Tan Tock Seng Hospital in Singapore, there were three suspected cases in a span of six months under the Department of Geriatric Medicine. It raises the concern as to whether a change in the recommended dosage of cefepime is needed. We also wanted to examine prescribing patterns of cefepime in the department and whether renal dose adjustments were appropriately done.

This is a department-approved quality improvement study. The objectives of the study were:

1. To screen for cases of cefepime-induced encephalopathy in the past one and a half years in the Department of Geriatric Medicine in Tan Tock Seng Hospital.
2. To identify other possible risk factors aside from renal impairment that can predispose elderly patients to this adverse effect.
3. To examine how physicians in our department exercise diligence in prescribing cefepime with regards to its indications and necessary renal dose adjustment.

2. METHODS

This is a retrospective and observational quality improvement study of the Department of Geriatric Medicine in Tan Tock Seng Hospital, Singapore. Case records of patients admitted to the department between March 2014 and September 2015 were retrieved. The pharmacy database was used to identify a total of 289 hospital episodes during which patients received cefepime within this time period.

Electronic medical records of each case were retrieved. The discharge summary, electronic inpatient medical record (eIMR), inpatient vital signs record and scanned notes were accessed. If scanned notes were not available, the paper case notes were retrieved from the medical records office.

For patients who received cefepime, premorbid function, cognition and pre-existing illnesses were recorded. The presence of chronic kidney disease (CKD) was charted. Estimated creatinine clearance was also calculated. The presence of stroke, seizure disorder and movement disorders were also charted.

For each patient, indication for cefepime, dose given and duration of treatment were recorded. We also verified if dose adjustments for renal function was performed based on the hospital's antimicrobial renal adjustment recommendation. Specifically, the recommended dose of cefipime was 2 grams every 12 hours if creatinine clearance was more than 30 ml/min, but 2 grams every 24 hours and 1 gram every 24 hours if creatinine clearance was 10 to 30 ml/in and less than 10 ml/min respectively.

The Aggregate Warning Score (AWAS) for each patient was reviewed to screen for any signs and symptoms of cefepime-induced neurotoxicity. AWAS is a scoring system based on systolic blood pressure, heart rate, oxygen saturation, respiratory rate, temperature and neurologic response. The scores enable the nurses to immediately recognize any clinical deterioration and it activates an algorithm of referral to the physicians. We charted the neurologic scores for 5 days after cefepime was administered.

Medical records of patients were reviewed and screened to look for possible signs of neurotoxicity during the course of cefepime and five days after the first dose.

After initial screening, the identified likely positive cases were reviewed by 6 investigators. The following criteria must be fulfilled to diagnose a case as cefepime-induced neurotoxicity: 1). neurologic symptoms including confusion, agitation, aphasia, myoclonus, hallucinations, convulsions and/or coma; 2). no alternative plausible etiology for the symptoms; and 3). clear temporal relationship between administration of cefepime and appearance of symptoms. Case records were carefully reviewed to ensure that the symptoms began after administration of cefepime. Other potential causes of these symptoms, such as new medications or drug interactions, were also ruled out. Resolution or improvement of symptoms after discontinuation of cefepime should also be observed.

The cases were labeled as Definite, Probable or Possible. When all 6 investigators agree that it is a case of cefepime-induced encephalopathy, it is considered a Definite case. If 5 investigators agree, it is a Probable case. If only 4 investigators agree, it will be labeled a Possible case. All other cases labeled by 3 investigators or less were removed from the pool.

3. RESULTS

A total of 289 hospital episodes during which cefepime may have been administered were identified from the pharmacy database. However, patients of 10 hospital episodes did not actually receive cefepime based on electronic medical records. For the 279 hospital episodes included, the patients' mean age was 87 years (standard deviation, SD: 6.5). Majority

of patients were cognitively impaired (n=174, 62%) and had CKD (n=157, 56%). The mean cefepime dose given per day was 2.7 grams. The mean duration of treatment was 3.2 days (SD: 2.8). Eighteen patients (6.45%) received higher dose of cefepime based on creatinine clearance, but none of them developed neurologic symptoms.

Indications for cefepime were: catheter-related urinary tract infection (UTI) (37.5%), non-catheter related UTI (58.5%), bacteremia (1.1%), respiratory infection (0.4%), intra-abdominal infection (0.7%) and other infections (1.8%). It was unexpected that cefepime was used more for non-catheter related UTI than catheter-related UTI.

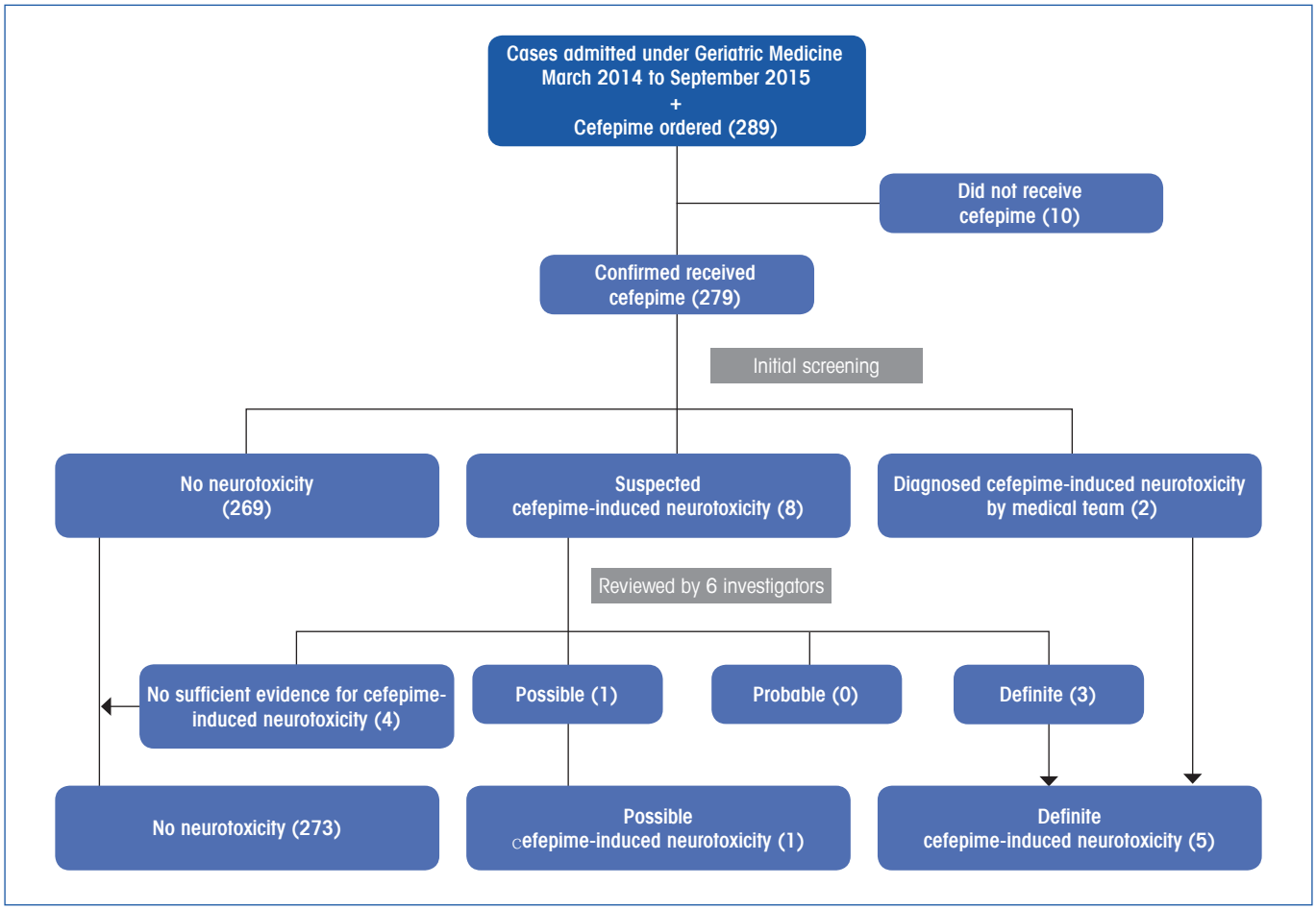
AWAS was not useful as a screening tool for change in sensorium. It was difficult to detect a change in sensorium within the 5 day period as the scores fluctuate within the same day. The scores did not reflect a change for those who presented with signs of cefepime-induced toxicity.

After screening the case records, 6 patients were identified to have cefepime-induced toxicity. This was 2.2% of the study population. There were five definite cases and one possible case. The characteristics of each case are summarized in Table 1.

Definite Case 1: A 90-year-old female who was admitted for fever. She had a background history of previous left parietal lobe infarct. Despite two days of empiric antibiotics for UTI, patient remained febrile. The antibiotic was then shifted to cefepime. She had renal impairment and the appropriate adjusted dose was administered. On the fourth day of cefepime, she developed decreased sensorium and slurring of speech. MRI of the brain did not reveal any acute infarcts. She received a total of 5 days of cefepime. Two days after stopping cefepime, her sensorium improved but still had slurring of speech upon discharge.

Definite Case 2: An 85-year-old female who was admitted for fever. She was initially treated for *E. coli* bacteremia from likely urosepsis and was given cefazolin. The first urine culture was negative. The second urine culture grew *Pseudomonas* which was not sensitive to cefazolin, but sensitive to cefepime. The antibiotic was then shifted to cefepime with dose adjustment based on her creatinine clearance. On the fifth day of cefepime, patient was observed to be staring blankly with focal jerking movements of the facial muscles and intermittent jerking of the extremities. MRI of the brain did not reveal any strokes. EEG was abnormal and the clinical impression was cefepime-induced encephalopathy. Cefepime

Figure 1. Methodology.



was administered for a total period of 6 days. Four days after stopping cefepime, convulsions resolved and sensorium improved.

Definite Case 3: A 91-year-old male who was admitted for gross hematuria. He had a background history of benign prostatic hyperplasia (BPH). He was treated for hemorrhagic cystitis and was given co-amoxiclav. An indwelling urinary catheter was inserted due to urinary retention. During the prolonged admission due to social issues, he developed fever. The clinical impression was catheter-related UTI and he was given cefepime. Four days after starting cefepime, he was noted to be dazed with episodes of decreased sensorium. He also had jerking movements of his right extremities. MRI of the brain was normal. EEG showed continuous diffuse slowing and triphasic waves, but no epileptiform activity. He was diagnosed as having cefepime-induced encephalopathy and antibiotics were changed. Six days after stopping cefepime, symptoms resolved.

Definite Case 4: An 89-year-old male who had a long-term indwelling urinary catheter for BPH. He presented with gross hematuria. He was treated for catheter-related UTI and given cefepime for 2 days. Dose adjustment was based on creatinine clearance. Three days after starting cefepime, he developed continuous chewing movements and right shoulder jerking. The clinical impression was cefepime-induced encephalopathy. MRI of the brain was normal. EEG revealed continuous diffuse slow activity with triphasic waves, but no epileptiform activity. Symptoms resolved 2 days after stopping cefepime.

Definite Case 5: An 85-year-old male who was admitted for cough and fever. He was initially given piperacillin-tazobactam for healthcare-associated pneumonia (HCAP). Urine culture revealed *Enterobacter* which was resistant to piperacillin-tazobactam, but sensitive to cefepime, amikacin, gentamicin and meropenem. The medical team shifted antibiotics to cefepime. Three days after starting cefepime, he developed mixed delirium. He had episodes of decreased sensorium, alternating with agitation. Brain imaging was normal, but EEG was abnormal. Symptoms resolved two days after stopping cefepime.

Table 1. Characteristics of patients with cefepime-induced neurotoxicity.

	Definite Case 1	Definite Case 2	Definite Case 3	Definite Case 4	Definite Case 5	Possible Case 1
Age/Gender	90/F	85/F	91/M	89/M	85/M	80/M
Premorbid function	ADL dependent Chair-bed bound	ADL independent Community ambulant	ADL independent Community ambulant	ADL dependent Bed bound	ADL independent Ambulates with WF	ADL independent On motorized WC
History of stroke	Previous infarct left parietal lobe	Lacunes in bilateral basal ganglia	None	None	None	Subdural bleed
History of seizure	None	None	None	None	None	None
CrCl (ml/min)	14.5	11.5	49.0	14.2	55.0	108.9
Dose per day (mg)	2	2	2	2	2	4
Duration of tx (days)	5	6	5	2	8	3
Latency period (days)	4	5	4	3	3	0.75
Symptoms	Decreased sensorium, confusion, slurring of speech	Decreased sensorium, confusion, convulsions	Decreased sensorium, confusion, aphasia, convulsions	Decreased sensorium confusion, myoclonus	Decreased sensorium confusion, agitation, mixed delirium	Confusion, agitation, mixed delirium
Brain imaging	No evidence of acute infarct	No acute infarct, intracranial hemorrhage or mass effect	No acute infarct, intracranial hemorrhage or mass effect	No acute infarct or intracranial haemorrhage is detected	No acute intracranial haemorrhage or territorial infarct	Not done
EEG	Not done	No normal background seen, continuous diffuse sharply contoured 3-5 Hz slow waves with superimposed fast activity	Continuous diffuse slowing and triphasic waves. No epileptiform activity	Continuous diffuse slow activity, absence of normal background rhythm, riphasic waves. No epileptiform activity seen	Background slow, intermittent diffuse slow activity, sharp transient in bifrontal region	Not done
Recovery period (days)	Unknown (Discharged slightly improved)	4	6	2	2	8
Outcome	Survived	Survived	Survived	Survived	Survived	Survived
Function at discharge	Premorbid levels	Declined	Declined	Premorbid levels	Declined	Declined

ADL: Activities of Daily Living.

Possible Case 1: An 80-year-old male who was admitted to the neurosurgical department for traumatic subdural hemorrhage (SDH) from a fall. He developed mixed delirium from SDH, electrolyte imbalances, acute retention of urine and sepsis. In view of his behavior issues, he was transferred to the Geriatric Medicine Department. Urine culture grew *Pseudomonas* and he was given three days of cefepime. Within a day of giving cefepime, his behavior seemed to be worse. Behavioural symptoms resolved 8 days after stopping cefepime.

In this case series, the mean latency period was 3 days which is shorter compared to other studies. The mean recovery period was 4 days.

Predominant symptoms suggestive of cefepime-induced neurotoxicity were confusion (n=6) and drowsiness or decreased sensorium (n=5). Other symptoms included myoclonus (n=2) and agitation (n=2). Three patients presented with convulsions and one of them had epileptiform activity noted on EEG. All of them survived. Four patients had decline in physical function at discharge while the other two did not.

Compared with the rest of the study population (Table 2), the group with cefepime-induced neurotoxicity had higher proportion of males and CKD. However, it was surprising to note that it had lower proportion with dementia or cognitive impairment. This group also received a lower mean daily dose of cefepime, but a longer duration of treatment.

Table 2. Characteristics of the study population.

	Cefepime-Induced Neurotoxicity (n=6)	Rest of Cohort (n=273)
Age, years, mean (SD)	87 (4.2)	87 (6.5)
Male gender, n (%)	4 (67)	131 (47)
CKD, n (%)	5 (83)	152 (55)
Stroke, n (%)	3 (50)	136 (50)
Seizure, n (%)	0 (0)	4 (1)
Dementia/cognitive impairment, n (%)	2 (33)	172 (63)
Daily cefepime dose, gram, mean	2.3	2.8
Cefepime duration, days, median	4.8	3.2
Inappropriately higher dose given, n (%)	0 (0)	18 (7)

4. DISCUSSION

Over a period of one and a half years, six cases of cefepime-induced neurotoxicity were identified out of 279 patients. Thus, the incidence was 2.2%, which is similar to 3% observed in another study.[1] The average cefipime dose administered for patients with cefepime-induced neurotoxicity was 2.5 g/day in previous studies.[2] For our study, the mean dose given for this group was 2.3 grams which is comparable.

The latency period in our study was 3 days, which is shorter than that noted in previous studies which was 5 days.[2,4,5] Previous studies have shown that recovery period was 24 to 48 hours.[6] In our study, the recovery period was 4 days.

The investigators anticipated that the antibiotic dosage for patients with cefepime-induced neurotoxicity may be higher than recommended. Of the six identified cases, none received inappropriately higher dosages of cefepime after considering renal adjustment. However, we noted that the median duration of treatment was longer for the group with neurotoxicity. This means that even though appropriate renal-adjusted doses of cefepime were administered, a longer duration of treatment may have predisposed to neurotoxicity. Thus, it is recommended that appropriate and timely de-escalation of cefepime should be practised.

It is already known that renal impairment predisposes patients to cefipime-induced neurotoxicity. Five of the 6 cases had CKD. We wondered whether history of previous stroke, seizure disorder, cognitive impairment or dementia would predispose patients to this condition. However, the small number of cases of neurotoxicity does not permit meaningful analysis to answer this question, although the proportions of these conditions in patients with and without this adverse effect do not suggest any clear predisposition.

Of the five definite cases identified, only two were diagnosed by the primary team to have cefepime-induced toxicity. The diagnosis was considered in two cases. For the other definite case, confusion and slurring of speech were attributed to likely new stroke even though brain imaging did not confirm this diagnosis. For the possible case, confusion and agitation were attributed to delirium secondary to UTI, retention of urine and constipation. It may be that the main challenge in detecting cefepime-induced neurotoxicity is lack of awareness of its possibility.

Our hospital's empiric antibiotic guidelines recommend administering cefepime for UTI with urinary catheter or neurogenic bladder and for UTI after urologic procedures. About one third of the study group had catheter-related UTI. It was surprising that cefepime was used more often for non-catheter related UTI. None of them underwent a urologic procedure, and the main indication for its use was treatment failure with other antibiotics.

5. CONCLUSION

Cefepime-induced neurotoxicity is an important

diagnosis to monitor for when this antibiotic is administered to elderly patients and those with renal impairment. Diligence in prescribing the correct renal-adjusted dose must be practiced. Since the duration of treatment may be an important factor in its occurrence, timely and appropriate de-escalation of antibiotics is important. If cefepime is to be administered for longer than 3 to 4 days, signs of cefepime-induced neurotoxicity should be closely monitored for.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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