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Cefepime en neuropsychiatric symptoms

Introduction

Previously, we have reported on a cluster of neuropsychiatric symptoms in patients with febrile neutropenia and treatment with cefepime [1,2].

Recently, José Martínez-Rodríguez en associates have reported in the American Journal of Medicine a retrospective survey on the incidence of non-convulsive status epilepticus, defined as epileptic activity on the EEG for at least 30 minutes, combined with decreased consciousness, agitation or disorientation but without seizures, in patients treated with cephalosporins[3]. They describe 10 patients with non-convulsive status epilepticus during or shortly after the use of cephalosporins. All patients had some degree of renal insufficiency (8 chronic and 2 acute), for which no dosage adjustment was applied. Six of them were treated with cefepime. The authors have reported their cases to the Catalan Pharmacovigilance Authority.

Reports

Until now, 6 cases of neuropsychiatric symptoms in relation with cefepime have been reported to Lareb. Five cases have been reported to the MEB previously. The sixth case was patient F, a woman with rheumatoid arthritis treated with methotrexate. She was admitted to the hospital because of fever, leukopenia, thrombopenia and pneumonia. Antibiotic treatment was started with cefepime. In the following three days consciousness decreased, finally resulting in coma. No cause could be found. Cessation of cefepime treatment followed and the patient recovered within 36 hours.

patient	gender age	dose (gram)	ECC (ml/min)	latency (days)	event	cessation	recovery (days)	remark
A	female 37	2 t.i.d.	75	5	anxiety, agitation, restricted awareness	yes	2	retrograde amnesia
B	female 45	2 t.i.d.	88	2	visual hallucinations	no	2	
C	male 57	2 t.i.d.	91	3	nightmares, anxiety, agitation, confusion, auditive hallucinations	yes	2-3	
D	female 55	2 t.i.d.	97	1	nightmares, visual hallucinations, cerebellar dysfunction	yes	1	negative rechallenge
E	male 32	2 t.i.d.	15	3	coma, seizures	yes	5	
F	female 75	1 t.i.d.	35	3	coma	yes	2	

In patients B, C, and D, anxiety, nightmares, hallucinations and cerebellar dysfunction developed within one to five days after start of the treatment with cefepime. They recovered within 3 days after cessation of cefepime.

The dosages and endogenous creatinin clearances according Cockcroft-Gault are tabulated. According the SPC of cefepime, dose adjustments are recommended in case of a creatinin clearance < 30 ml/min.

No EEG was conducted in any of the six patients. Therefore, it can not be ruled out that patients A and F have had a non-convulsive status epilepticus. Patient E may have had a seizure followed by a non-convulsive status epilepticus.

Other sources of information

Literature

Dixit et al. have published a case report concerning two patients with status epilepticus during high-dose cefepime. Symptoms resolved completely after withdrawal of cefepime[4]. Saurina et al. published two cases of non-convulsive status epilepticus in patients with advanced chronic renal failure who received cefepime at doses corrected for the degree of renal function according to the SPC. Clinically, they suffered from disorientation, loss of attention, and later appearance of myoclonus. In both cases the electroencephalogram (EEG) was compatible with non-convulsive epileptic status. After cefepime withdrawal there was a clinical remission of symptoms and normalization of the EEG[5].

Medline shows 5 hits on status epilepticus/chemically induced and cephalosporins, including 3 publications on non-convulsive status epilepticus (all mentioned above).

Databases

In the WHO-database, the association between cefepime and coma shows a statistically significant reporting odds ratio (4,03 with 95% confidence intervals: 1.80 - 9.04), in contrast with the associations between other cephalosporins and coma. Taking into account the number of associations between cefepime and coma in this database (n=6), the Dutch contribution is too substantially to consider this disproportionality as supporting for causality.

Mechanism

The epileptogenic effect of cephalosporins is well-known. However, the non-convulsive status epilepticus must be considered as a serious pitfall in the diagnostic work up of a patient with coma e.c.i. Any patient with unconsciousness for unknown reasons and during treatment with cefepime should undergo an EEG to rule out a status epilepticus.

Cefepime easily transfers the blood brain barrier. Therefore, CNS adverse events are pharmacologically plausible. Our cases and the cases from reference 5, suggest that dose adjustments for renal insufficiency offer insufficient protection against CNS-adverse events.

Discussion and conclusion

The occurrence of status epilepticus during treatment with cefepime seems to be related to renal insufficiency. Dose adjustment according to the SPC may be insufficient to protect against this adverse event. This may be due to the recommendation in the SPC, but also to patient characteristics with influence on serum and cerebrospinal liquor pharmacokinetics.

In any patient with neuropsychiatric symptoms, and especially unconsciousness, an EEG should be made to rule out a status epilepticus.

Quality of the signal: Our cases are supported by literature data, disproportionality in our database. The disproportionality in the WHO-database is mainly based on our data and should therefore be ignored. Pharmacologically, the adverse event may be due to insufficient adjustment for renal insufficiency and presumably also to changes in the permeability of the blood brain barrier.

References

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