Visual hallucinations related to use of ertapenem☆

Alucinaciones visuales en relación al uso de ertapenem

Use of carbapenem has expanded in the last few years due to increased microbial resistance. This increase in use has made it easier to observe rare side effects in clinical practice, such as those we describe here.

We present the case of a 76-year-old woman with a personal history of renal transplant due to C virus-related liver disease. She currently presents micronodular cirrhosis and chronic kidney disease (CKD) due to focal and segmental proliferative glomerulonephritis. Her baseline creatinine level was approximately 4 mg/dL. She had been fitted with a pacemaker due to a second degree arterioventricular block. Her history also includes chronic obstructive pulmonary disease and IgG-kappa monoclonal gammopathy of unclear significance. Our patient had a permanent urinary catheter and double J stent due to obstructive uropathy; she had experienced several urinary tract infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*). After the last episode, she was discharged under treatment with intramuscular ertapenem (1 g every 24 h) to be administered on an outpatient basis.

Forty-eight hours after discharge, our patient came to the emergency department due to visual hallucinations, behavioural changes, and gait instability with no other focal neurological signs. No signs of infection were observed at any level and the only change in medication was the addition, 48 hours before, of 1 g of intramuscular ertapenem every 24 hours. During the first 24 hours after admission, the patient suffered a focal seizure with right gaze deviation and disorientation. Physical examination revealed disorientation in time, but orientation in place and person. She showed inappropriate and disinhibited behaviour, and was unable to remain either standing or seated. The rest of the examination did not yield any relevant results.

We requested a complete blood test which revealed a creatinine level of 3.9 mg/dL, gamma-glutamyl transferase at 580 U/L, alkaline phosphatase at 235 U/L, and lactate dehydrogenase at 258 U/L. All other parameters were within normal ranges. Cerebrospinal fluid obtained by lumbar puncture was analysed and yielded 0 cells/mm^3, 0 red blood cells/mm^3, a glucose level of 69 mg/dL, and proteins at 29.8 mg/dL. We also performed a brain computed tomography (CT) without intravenous contrast, which only showed changes related to leukoaraiosis. An electroencephalogram (EEG) displayed no epileptogenic activity.

In absence of any other plausible explanation, and given that the patient's dose of ertapenem was not adjusted to her stage of kidney disease (creatinine clearance < 30 mL/min), we decided to replace it with a course of meropenem dosed at 500 mg every 24 hours. All neurological symptoms disappeared once the antibiotic had been substituted.

Secondly, we present the case of a 44-year-old man whose only relevant medical history was pneumonia due to *Legionella*. The patient was seen at the emergency department due to fever that had lasted 48 hours, accompanied by irritative urinary syndrome, haematuria progressing over 7 days, and pain located at the left renal fossa. He was afebrile upon physical examination; his abdomen was painful to the touch in the left flank and iliac fossa, with no signs of peritoneal irritation after a positive fist percussion test on the left side. A blood test registered leukocytosis of 19,800 cells/mm^3 with a left shift, and reactive C-protein (PCR) of more than 190 mg/dL. Urine tested positive for nitrites and red blood cells, and sediment contained 20-50 leukocytes per field. Bacteria could be isolated from the sediment. Increased levels of ESBL producing *E. coli* were observed in both urine and blood cultures, so the patient was treated with ertapenem dosed at 1 g every 24 hours. While hospitalised, our patient started to present photopsias, so we decided to perform a brain CT which yielded normal results.

Since photopsias disappeared once the ertaperem dose had been reduced (to 500 mg every 24 h), we concluded that the alteration was a dose-dependent neurotoxic effect.

Ertapenem is a novel drug from the carbapenem family whose main advantage is that it can be administered intramuscularly in a single dose.[1,2] This can make hospital stays shorter for patients who need prolonged antibiotic treatment and present no other motives for hospitalisation.

Neurotoxicity has been described in patients with advanced CKD who were not undergoing haemodialysis.[3] Their symptoms include visual hallucinations, asterixis, myoclonic jerks, and cognitive impairment. Despite receiving doses adjusted to their level of kidney function (500 mg/day), these patients had their drug plasma levels tested after symptom onset. Since measurements revealed a dose much higher than the minimum inhibitory concentration (MIC), the medication was withdrawn and patients were treated with haemodialysis. Nevertheless, symptoms persisted for 2 more weeks. This suggests that patients with advanced CKD should receive doses even lower than those recommended to avoid neurotoxicity, which is favoured by the structure and pharmacodynamic characteristics of ertaperem, by its high liposolubility which results in easy penetration of the central nervous system, and by other factors.

In contrast, another 2 patients, both older than 70 in this case, exhibited altered mental state while undergoing treatment with ertapenem.[4] One experienced slurred speech and miosis one week after treatment onset. Symptoms disappeared when the drug was withdrawn, but appeared again when the same treatment was resumed. The other patient who presented CKD reported delirium and drowsiness which progressed to such an extent that orotracheal intubation and mechanical ventilation were required. Two days after the drug was suspended, the patient's mental state returned to normal and support measures were removed.

In light of the adverse effects that we observed in our department, we applied the Naranjo algorithm[5] to assess causality of a drug-related adverse effect; it determined that the association was probable in both cases.

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The literature on the subject suggests an association between the neurotoxicity generated by beta-lactam antibiotics and their ability to interact with gamma-aminobutyric acid (GABA) receptors.[6] However recent studies in rats suggest the involvement of other factors, such as increased release of excitatory aminoacids,[7] which has yet to be demonstrated.

Considering the above, we conclude that in patients who are receiving treatment with carbapenem and present neurological alterations or altered mental state, especially in cases of patients with CKD or elderly patients, we should consider an adverse effect of the drug to be a potential cause after ruling out other possibilities. According to the pattern observed in these cases, symptoms can persist up to 2 weeks after suspension of the drug.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Logopenic progressive aphasia associated with idiopathic Parkinson's disease☆,☆☆

Afasia progresiva logopénica asociada a enfermedad de Parkinson idiopática

Dear Editor,

Primary progressive aphasia is a clinical syndrome characterised by a language deficit of neurodegenerative origin with no other cognitive manifestations, at least during the initial stages.[1] Three clinical variants have been described to date (nonfluent, semantic, and logopenic), each associated with its distinct topography and anatomical pathology.[3] Of the 3 variants, logopenic aphasia is mainly associated with Alzheimer disease, and it is considered an atypical form of AD onset.[1] However, the association between logopenic aphasia and Alzheimer disease is still a matter of debate in the literature. Associations with other diseases have been found in a high percentage of cases in studies using molecular imaging, cerebrospinal fluid biomarkers, or anatomical pathology findings.[3,4] Furthermore, cognitive impairment and dementia associated with Parkinson's disease are regarded as frequent. They are characterised by executive and/or memory deficits, while language typically remains preserved.[5] We present the case of a patient with idiopathic Parkinson's disease who developed symptoms of progressive logopenic aphasia. Her symptoms finally progressed to generalised dementia with biomarkers of Alzheimer disease, thereby supporting the idea that this type of aphasia is a marker of Alzheimer disease.

Our patient is a 65-year-old woman with high blood pressure and dyslipidaemia, who in 2009 was diagnosed with idiopathic Parkinson's disease after a one-year period in which she displayed slowness and tremor. Neurological examination revealed rigidity, bradykinesia, and resting tremor predominantly on the right side. She responded favourably to levodopa and subsequently developed motor fluctuations. She also presented REM sleep behaviour disorder. Since mid 2012, the patient began reporting increasing difficulty finding words without any associated memory impairment or behaviour disorder. She experienced no hallucinations and her neurological examination did not

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