Ertapenem-Induced Delirium

Delirium Induzido pelo Ertapenem

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RESUMO

A neurotoxicidade é um efeito iatrogénico incomum relacionado com carbapenemes, tipicamente manifestado através de convulsões ou *delirium* hiperativo. Relatamos o caso de uma doente de 89 anos com história de hipertensão arterial e doença renal crónica internada por taqueobronquite aguda e anemia devida a doença diverticular. Como intercorrência apresentou cistite aguda por *Klebsiella pneumoniae* produtora de ß-lactamases de espectro estendido, tendo iniciado ertapenem endovenoso. Ao segundo dia dessa antibioterapia manifestou alucinações visuais seguidas de estado de inatenção e letargia, sugestivo de *delirium* hipoativo. Suspeitámos de neurotoxicidade ao ertapenem. Com a substituição por meropenem, assistiu-se a melhoria com reversão sintomática após 72 horas. Revimos casos de alucinações induzidas pelo ertapenem e salientamos aspetos farmacocinéticos nomeadamente a disfunção renal e a hipoalbuminemia potenciadores da encefalopatia. Apesar de raro, os clínicos devem estar alerta para a neurotoxicidade não-convulsiva relacionada com o ertapenem. O reconhecimento atempado facilita a reversão e previne complicações deletérias.

PALAVRAS-CHAVE: Alucinações/induzido quimicamente; Delírio/induzido quimicamente; Ertapenem/efeitos adversos

ABSTRACT

Neurotoxicity is an unusual iatrogenic effect associated with carbapenems, typically manifested as seizures or hyperactive delirium. We present an 89-year-old female patient with a medical history of hypertension and chronic kidney disease who was admitted for acute tracheobronchitis and anemia related to diverticular disease. As a complication, she developed acute cystitis caused by extended spectrum ß-lactamases producing *Klebsiella pneumoniae*, so intra-

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venous ertapenem was started. On the second day of antibiotic therapy, the patient manifested visual hallucinations followed by an inattentive and lethargic state suggestive of a hypoactive delirium. An ertapenem-induced neurotoxicity was suspected. Upon substitution by meropenem, the patient improved, and symptom reversal occurred after 72 hours. We present a review of ertapenem-induced hallucinations and address pharmacokinetics aspects namely renal dysfunction and hypoalbuminemia that could potentiate encephalopathy. Although rare, clinicians should be aware of non-seizure ertapenem related neurotoxicity. Ready recognition can lead to rapid improvement and prevent dire outcomes.

KEYWORDS: Delirium/chemically induced; Ertapenem/adverse effects; Hallucinations/chemically induced

INTRODUCTION

Carbapenems are ß-lactam antibiotics used to treat multidrug-resistant bacteria. They have been associated with seizures occurrence, for they are able to cross the blood-brain barrier and interact with the ß-aminobutyric acid receptor. Ertapenem was introduced in the 2000 decade. Main clinical indications include central nervous system, urinary tract, intra-abdominal, and pulmonary infection. Its 4-hour half-life allows once day intravenous (IV) dosage. So, its usage raised in the last two decades, due to mentioned pharmacological advantage and to increasing emergence of multidrug-resistant bacteria. Ertapenem shares the tissue penetration characteristics and neurologic interaction with other prior introduced carbapenems.[1]

Iatrogenic encephalopathy manifestations are not limited to seizures, and other manifestations can take place. We report a patient who developed visual hallucination followed by hypoactive delirium during a course of ertapenem.

CASE REPORT

An 89-year-old female patient presented to the Emergency Department with coughing, mucopurulent sputum, fatigue, and pallor. Her known medical history included hypertension, stage 2 chronic kidney disease, and mild cognitive impairment requiring help with hygiene but able to walk unassisted. She was usually prescribed with amlodipine 5 mg q.d., lisinopril 20 mg q.d.

On initial exam, patient blood pressure was 136/78 mmHg, heart rate 71 beats per minute and tympanic temperature 37.0˚C. She was oriented to person, place, and situation. No adventitious lung sounds were discernible on auscultation. Skin and mucosa were pale. Feces had hematochezia characteristics. No masses were found on abdominal palpation or ano-rectal examination. Elevated acute phase reactants, renal dysfunction and low hemoglobin were evident (Table 1). Chest radiograph showed no signs of condensation or nodules.

After a 7-day course of amoxicillin+clavulanate 1200 mg t.i.d., acute tracheobronchitis symptoms resolved. Colonoscopy revealed diverticular disease as the cause of the anemia. Abdominopelvic computed tomography did not find signs of diverticulitis nor neoplasm. She received 750 mg of IV ferric carboxymaltose. Dietary changes were implemented, and the patient was referred to Gastroenterology clinic for further follow-up.

On the tenth day, patient complained of dysuria. An extended-spectrum ß-lactamase-producing *Klebsiella pneumoniae* was isolated in the urine. Upon acute cystitis diagnosis IV ertapenem 1000 mg q.d. prescription was started.

Despite favorable urinary symptoms response, on the twelfth day, the patient exhibited a confusional state comprising visual hallucination that she described as animals flying inside the room sic. Initially no other cognitive functions were affected. She had no fever or signs of meningeal irritation. No pathological signs during photomotor, oculocephalic, and osteotendinous reflexes testing were noted. There was no change in muscle strength or tone, myoclonus or asterixis. Analytical study did not point to any etiology. Cranioencephalic computed tomography revealed no lesions.

On the thirteenth day, patient became inattentive and lethargic. Hypoactive delirium diagnosis was considered upon Neurology and Psychiatry consultations. Suspecting toxic encephalopathy, we replaced ertapenem with meropenem (1000 mg t.i.d. for 4 days). Neurologic state improved and symptoms ceased after 72 hours of the antibiotic switch. Facing favorable reversal, further testing was halted. During remaining hospital stay and until office re-evaluation on the 14th day after discharge, the neurologic dysfunction did not recur.

DISCUSSION

In this case an 89-year-old female patient, who received ertapenem to treat an extended-spectrum ß-lactamase-producing *Klebsiella pneumoniae* urinary tract infection,

developed hallucinations followed by hypoactive delirium. *De novo* neurological symptoms associated with antibiotic initiation in addition to syndromic resolution consequent to its suspension, without needing further interventions, suggests iatrogenic encephalopathy by ertapenem.

We performed a PubMed search for similar cases. Table 2 summarizes the twenty cases found.[2-15] Like our report, the majority aged 65 years or older.[2-4,6-12,14,15] Symptom onset often occurred between the third and seventh day of ertapenem exposure.[2-7,9,11,12,14,15] In one report symptoms manifested after 42 days of exposure.[10] Unlike ertapenem-induced seizure cases, in which a past history of epilepsy, dementia, cerebrovascular disease or head trauma is often required, hallucination cases do not required such medical history. After drug discontinuation, it took between 2 to 14 days for the symptoms to regress.[3-11,13-15] In one case, ertapenem was not interrupted and cognitive dysfunction lasted 21 days after antibiotic course completion.[12] Although no report culminated in patient death, two cases required intensive care. In both ertapenem administration was perpetuated leading to delirium refractive to multiple therapeutic try-outs until discontinuation and clinical improvement.[8,15]

In contrast to previous reported cases, where hyperactive delirium symptoms, such as confusion, agitation and hallucination, are given emphasis, our patient exhibited a shift to hypoactive delirium. This subtype is often undiagnosed or later considered upon several inconclusive time-consuming diagnostics exams.

Ertapenem pharmacokinetic determining factors should be considered. Glomerular filtration rate was inferior to 30 mL/kg/1.73 m^2 in nine cases.[2-4,7,9,12,14] Our patient's renal function oscillated, reaching near dose reduction cut-off when applying Cockcroft-Gault formula (Table 1). Authors expressed concern about newer equations undervaluing renal impairment when compared to classical ones in elder patients.[10,15] Moreover, some authors argue in favor of the need for dose adjustment in 30-60 mL/kg/1.73 m^2 in order to reduce the risk of neurotoxicity.[5,6] One author quantified serum drug accumulation with the manufacturer recommended dose for end stage renal failure.[7] Another author warns of a special population, post-spinal cord injury status, whose renal function estimation requires distinct equation.[13] In our case, hypoalbuminemia was also present (Table 1). In literature it was described in seven reports.[4,7,8,10,11] Ertapenem binds reversibly to circulating proteins and hypoalbuminemia increases its volume of distribution.

TABLE 1. Analytical parameters evolution.

Parameter	Admission	Introduction of ertapenem (10th day of admission)	Suspension of ertapenem (13th day of admission)
Leukocytes/µL	12,400	10,300	7,700
Hemoglobin (g/dL)	8.1	9.0	9.1
Hematocrit (%)	24.4	27.4	28.2
Mean corpuscular volume (fL)	89	90.2	91.7
Mean corpuscular hemoglobin (pg)	29.5	29.7	29.7
Creatinine (mg/dL)	1.45	0.78	0.99
eGFR CKD-EPI (mL/min/1.73 m^2)	32	68	51
CC-CGF (mL/min)	25	46	36
Na+ (mEq/L)	141	133	137
K+ (mEq/L)	4.7	4.6	4.5
CRP (mg/dL)	170	77	24
Albumin (g/L)	-	26	29
Iron (µg/dL)	-	-	19
Transferrin (mg/dL)	-	-	153.3
Transferrin saturation (%)	-	-	9.9
Total iron binding capacity (mg/dL)	-	-	191.7
Ferritin (ng/mL)	-	-	97.8
Folic acid (ng/mL)	-	-	10.5
Vitamin B12 (pg/mL)	-	-	1.001

CC-CGF - creatinine clearance according to Cockcroft and Gault formula; **CKD-EPI -** equation of the Chronic Kidney Disease Epidemiology Collaboration; **RCP–C** - reactive protein; **eGFR** – estimated glomerular filtration rate.

The consequent blood-brain barrier passage facilitation and central nervous system accumulation can potentiate neurotoxic effect.[1]

The presented case reminds us that ertapenem neurotoxicity can occur through non-convulsive symptoms like hallucination and even hypoactive delirium. The latter is more subtle and requires a high degree of clinical suspicion for prompt diagnosis. Renal dysfunction and/or hypoalbuminemia are contributive factors. Early recognition and ertapenem discontinuation often allow symptom reversal sparing unnecessary investigations and preventing dire outcomes.

TABLE 2. Delirium induced by ertapenem cases review.

Author (year)	Gender/ age	Symptoms	Creatinine clearance	Ertapenem completed days until symptoms	Ertapenem suspension	Days after ertapenem suspension until symptoms resolution	Comorbidities	Diagnosis	Death occurrence
Duquaine *et al* (2011)[2]	M / 70	Confusion, hallucinations, paranoia	15-30	5	Yes	NR	Smoking, alcoholism, cystectomy due to neoplasia	Intestinal occlusion	No
Wen *et al* (2013)[3]	F / 78	Hallucinations, asterixis	< 15	4	Yes	14	CKD	Acute cholecystitis	No
	F / 70	Hallucinations, asterixis	< 15	5	Yes	14	CKD	Arteriovenous fistula infection	No
Shea *et al* (2013)[4]	F / 84	Confusion, incoherent speech, nability to recognize familiar people, visual hallucinations	< 15	7	Yes	14	AHT, CKD	UTI	No
Oo *et al* (2014)[5]	M / 54	Persecutory delirium, hallucinations	30-60	5	Yes	10	DM, CKD	Diabetic foot infection	No
	M / 48	Disorientation, visual and auditory hallucinations	> 90	10	Yes	3	Major depression	Infected open fracture	No
Padilla-Peinado *et al* (2014)[6]	F / 76	Visual hallucinations, agitation, gait instability	30-60	2	Yes	2	HCV, liver transplant, focal segmental glomerulopathy, COPD, MGUS	UTI	No
Lee *et al* (2015)[7]	M / 72	Disorientation, incoherent speech, agitation, visual hallucinations	HD	5	Yes	7	Chronic glomerulonephritis	Incarcerated inguinal hernia	No
	F / 79	Agitation, visual hallucinations	HD	3	Yes	7	Chronic glomerulonephritis	Intestinal occlusion	No
	F / 73	Visual hallucinations, cognitive dysfunction	HD	7	Yes	8	Chronic interstitial nephritis	Arteriovenous fistula infection	No
Apodaca *et al* (2015)[8]	F / 42	Hallucinations, confusion, myoclonus	30-60	7	Yes	2	Alcoholic cirrhosis	Cellulitis	No
Ohlmann *et al* (2015)[9]	M / 68	Visual hallucinations, extrapyramidal syndrome	15-30	16	Yes	3	CKD	UTI	No

Author (year)	Gender/ age	Symptoms	Creatinine clearance	Ertapenem completed days until symptoms	Ertapenem suspension	Days after ertapenem suspension until symptoms resolution	Comorbidities	Diagnosis	Death occurrence
Veillette *et al* (2016)[10]	M / 71	Disorientation, hallucinations, suicidal ideation	30-60	42	Yes	1	Obesity, AHT, DM, HF, CKD	Diabetic foot infection	No
Sutton *et al* (2017)[11]	M / 67	Hallucinations, incoherent speech, asterixis	60-90	5	Yes	2	Non-Hodgkin's Lymphoma, AHT, AF, DM, ankylosing spondylitis, esophagitis	Vertebral abscess	No
Almorza *et al* (2016)[12]	M / 73	Visual and auditory hallucinations, persecutory delirium, myoclonias	< 15	4	No	21	CKD, Parkinson's disease	UTI	No
Patel *et al* (2018)[13]	M / 59	Visual hallucinations	> 90	10	Yes	6	Spinal cord injury, COPD, hypothyroidism, AHT, hyponatremia, OSAS, neurogenic bladder	UTI	No
	M / 90	Confusion, visual hallucinations	30-60	9	Yes	6	Spinal cord injury, AHT, pressure ulcer, glaucoma, alcoholism	Osteomyelitis	No
	M / 72	Visual hallucinations	60-90	1	Yes	2	Spinal cord injury, DM, cocaine addiction, COPD	Osteomyelitis	No
Tahseen *et al* (2019)[14]	F / 57	Visual and auditory hallucinations	HD	4	Yes	3	Psychiatric disorder	Sepsis after hemorrhoidal embolization	No
Adams *et al* (2020)[15]	M / 58	Disorientation, visual hallucinations, drowsiness, coma	30-60	5	Yes	2	Stroke, AMI, AHT, DL, CKD	Empyema	No

AF – atrial fibrillation; **AHT** – arterial hypertension; **AMI** – acute myocardial infarction; **CKD** – chronic kidney disease; COPD – chronic obstructive pulmonary disease; **DL** – dyslipidemia; **DM** – diabetes *mellitus*; F – female; **HCV** – hepatitis C virus; **HF** – heart failure; **M** – male; **MGUS** – monoclonal gammopathy of uncertain significance; **NR** – not reported; **OSAS** – obstructive sleep apnea syndrome; **UTI** – urinary tract infection.

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