

COLISTIN INDUCED NEUROTOXICITY: A CASE REPORT AND REVIEW OF LITERATURE

NEUROTOXICIDADE INDUZIDA PELA COLISTINA: RELATO DE CASO E REVISÃO DE LITERATURA

Monique Lírio¹ Gabriela Aguiar² Silvana Ultchak Spínola³ Ana Verena Mendes⁴ Maria Goreth Barberino⁵

ABSTRACT

Objective: To describe a case of neurotoxicity associated to Colistin.
Case description: A 29-year-old black male under treatment for urinary tract infection with identification of *Klebsiella pneumoniae* in urine culture resistant to all carbapenem antibiotics, presented visual turbidity, paresthesia on the face and upper left limb, slowed and discordant speech in the fourth day of Colistin use. Symptoms improved after reduction of the dose of colistin with adjustment for renal function, with complete reversion after discontinuation of the drug.
Conclusions: Colistin-mediated neurotoxicity must be suspected in patients with altered mental status of unknown etiology and therapy promptly interrupted.

Keywords: Colistin, neurotoxicity, review

RESUMO

Objetivo: Descrever um caso de neurotoxicidade associada à Colistina.
Descrição do caso (desnecessário repetição): Um homem negro de 29 anos sob tratamento para infecção do trato urinário com identificação de *Klebsiella pneumoniae* (escrever corretamente) em cultura de urina resistente a carbapenêmicos, apresentou turvação visual, parestesia em face e membro superior esquerdo, discurso lento e discordante no quarto dia de uso da Colistina. Os sintomas melhoraram após a redução da dose de colistina com ajuste para a função renal, com reversão completa após a descontinuação do fármaco.
Conclusões: A neurotoxicidade mediada por colistina deve ser suspeitada em pacientes com estado mental alterado de etiologia desconhecida e a terapia prontamente interrompida.

Palavras-chave: Colistina, neurotoxicidade, revisão

¹Médica assistente do Serviço de Infectologia, Hospital São Rafael, Salvador, Bahia, Brasil

²Médica residente do Serviço de Clínica Médica Hospital São Rafael, Salvador, Bahia, Brasil

³Médica assistente do Serviço de Infectologia, Hospital São Rafael, Salvador, Bahia, Brasil

⁴Coordenadora do Serviço de Infectologia, Hospital São Rafael, Salvador, Bahia, Brasil

⁵Coordenadora do Serviço de Microbiologia, Hospital São Rafael, Salvador, Bahia, Brasil

Endereço para correspondência: Dra. Monique Lírio Infectious Diseases Department. Avenida São Rafael, São Marcos Salvador, Bahia, Brazil
monique.lirio@yahoo.com.br telephone: (71) 3409-8000

INTRODUCTION

Polymyxin class antibiotics are polypeptides discovered in 1947 with potent Gram negative action and are used in clinical practice in the forms of polymyxin B and E, known as colistin. This drug class was widely used in the 1960s, but between the 1970s and 1980s its use was virtually abolished because of the side effects¹. Over the past 10 years, the advent of multi-resistant gram-negative microorganisms (MDR), such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*, have brought back the use of polymyxins (polymyxin B and Colistin) as potential therapeutic agents²

Nephrotoxicity is the most common and well described side effect of Colistin, characterized by the onset of renal injury, leading to acute renal failure and is considered as the major limitation of this class. Nevertheless, the occurrence of other toxicities related to colistin, such as neurological symptoms, have been described^{3,4}.

Colistin-mediated neurotoxicity has been described in the literature in fewer cases than renal injury and is characterized by various effects such as peripheral and facial paraesthesia, ophthalmoplegia, difficulty in swallowing, vertigo and respiratory apnea^{4,5} possibly with low dose colistin. A 47-year-old hypertensive female with chronic kidney disease-5 with sepsis on colistimethate sodium 1 million units (80 mg).

Herein, we present a case of encephalopathy and peripheral neurological symptoms (as parestesias podem ser de natureza central, para serem de origem periférica o exame neurológico deveria mostrar alguma alteração como arreflexia profunda, hipoestesia com alteração típica de raiz ou nervo, ou melhor, ainda com distúrbio na eletroneuromiografia) related to the the administration of colistin.

CASE REPORT

A 29-year-old black male with history of paraplegia, osteomyelitis of the right femur, chronic trochanteric decubitus ulcer, neurogenic bladder and recurrent urinary tract infection presented with purulent urinary discharge and fever. In urine culture, *Klebsiella pneumoniae*, identified by MALDI TOF (BioMérieux, Marcy l'Etoile, France), was isolated. The susceptibility test showed resistance to all carbapenem antibiotics, with meropenem MIC > 32 ug / m Land sensibility to colistin, tigecyclin and amikacin. Blood cultures were negative. Renal function was normal at the beginning of t?. Renal function was normal at

the onset of treatment with intravenous colistin (5mg/kg loading dose, followed by 2,5mg/kg BID and amikacin 15/mg/kg daily).

On the second day of treatment, he presented nausea and vomiting. Laboratory tests showed an increase of 0.2 in creatinine levels, but still within the normal range. The next day, the patient presented mental confusion after infusion of the nocturnal dose, with spontaneous resolution. On the fourth day of treatment, he evolved with visual turbidity, paresthesia on the face and upper left limb, slowed and discordant speech. There were no changes in muscle strength, reflexes and cranial nerves. Skull CT was normal (Figure 1).(sendo normal não há necessidade de mostrar a foto: ocupa espaço e nada acrescenta ao trabalho) New laboratory tests showed increased Creatinine (3,4 mg/dl) and potassium (6,0 mmol/L) levels. Due to renal dysfunction, amikacin was replaced for double carbapenem therapy (Ertapenem 1g/daily, followed by Meropenem 2g QID) and Tigecyclin (100mg loading dose followed by 50mg BID). Symptoms improved after reduction of the dose of colistin with adjustment for renal function, with complete reversion after discontinuation of the drug.

LITERATURE REVIEW

METHODS

Data for this review were obtained through literature searches of publications included in PubMed from 2006 to 2017 and references cited in relevant articles. The main search terms used in searches were 'polymyxin', 'colistin', 'adverse effects', 'neurotoxicity' and 'toxicity'. Also, secondary search was performed through the references of the articles found. Only English language papers were reviewed.

RESULTS

Table 1 summarizes the available publications reporting data regarding the incidence of colistin mediated neurotoxicity.

Neurotoxicity is a side effect of colistin much less described than nephrotoxicity and is resolved upon discontinuation of therapy. The incidence of neurotoxicity (most paresthesia) reported with the use of polymyxin has been reported to be approximately 7% in recent studies⁶. Intrathecal administration is related to a higher incidence with a incidence of 20% of meningeal irritation and seizures³. In the other cases, the most frequente experienced neuro-

logical adverse events were paraesthesias that occurred in approximately 27% and 7.3% of patients receiving intravenous and intramuscular colistimethate, respectively³. Less common symptoms included diplopia, ptosis, nystagmus, hallucinations, ataxia, seizures and partial deafness⁷.

Similar to nephrotoxicity, the risk of neurotoxicity is associated with increased exposure to the drug, such as longer duration of therapy or increased dose. Other risk factors for neurotoxicity include hypoxia and use of concomitant medications such as sedatives, anesthetics, muscle relaxants, narcotics or corticosteroids⁶. Also, patients with renal insufficiency or myasthenia gravis are at increased risk of developing neuromuscular block and respiratory paralysis³.

Few studies have evaluated the mechanism of colistin-induced neurotoxicity. Behavioral changes, muscle weakness and ataxia were observed in mice and rats exposed to Colistin⁸. Axonal degeneration and demyelination were also reported when mice were intravenously administered with 15 mg / kg / day colistin for 7 days⁹. Colistin-induced electrophysiological changes *in vivo* are not well elucidated.

In the case reported herein as well as in the reviewed cases, all patients had a full recovery of neurologic symptoms after discontinuation of colistin and additional therapies.

DISCUSSION

The emergence of multidrug resistant gram-negative bacteria in the recent decade has led to the revival of polymyxin antibiotics and has also brought concern to its adverse effects¹⁰. Colistin associated neurotoxicity, although still a rare effect, has been described in some case reports. The neurological findings are variable. Some individuals present mild to moderate symptoms^{11,12}, as our patient, involving visual turbidity, paresthesia and slowed speech. Nevertheless, severe cases of neurotoxicity have been reported, including respiratory muscle paralysis^{1,2}

The proposed mechanism of colistin associated neurotoxicity is a noncompetitive myoneuronal presynaptic

blockade of acetylcholine release that may be enhanced by hypocalcemia-induced prolongation of depolarization¹³ ISBN : "1460-2091 (Electronic. Risk factors for developing neurological side effects include abnormal renal function and concomitant drug therapies including other neurotoxic drugs such as anesthetics, aminoglycosides, corticosteroids, and muscle relaxants¹⁴.

Herein, we reported a case of neurotoxicity in a patient without previous impairment of the central nervous system. Although he presented normal renal function at the onset of treatment, he was doing concomitant use of amikacin, which may have contributed to worsening renal function and colistin neurological side effects. Neurological diseases such as stroke were excluded in this patient. He was not receiving any steroids or muscle relaxants.

Studies that clarify the optimal dosing of colistin are unclear. Thus, regular monitoring of renal function as well as monitoring the neurological status is important to prevent and manage the toxicities associated with colistin use. In all cases, should drug be discontinued and there is no reversal agents¹⁴. As this reaction can be reversible, continuous renal replacement therapy or hemodialysis may be a reasonable option to help in patients with acute renal failure or with high serum levels of polymyxins¹. Prognosis of adverse colistin toxicity is generally good and once the agent is discontinued recovery may take up to 72 h⁴.

Also, it is important to point that in our review, data from the recent studies suggest that the frequency of toxicity resulting from the use of polymyxins is lower and less severe when compared to what has been previously described in 60s-70s^{10,14}. This discrepancy may be due the avoidance of co-administration of nephrotoxic and/or neurotoxic drugs, careful dosing, as well as more meticulous management of fluid and electrolyte abnormalities and use of critical care practices^{1,14}.

In conclusion, although less frequent than previously described, the diagnosis of polymyxin-mediated neurotoxicity should be suspected in patients with altered mental status of unknown aetiology. Prompt interruption of therapy is indicated to avoid any fatal consequences.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest.

REFERENCES

1. Wadia S, Tran B. Colistin-mediated neurotoxicity. *BMJ Case Rep.* 2014;2014:1-2. doi:10.1136/bcr-2014-205332.
2. Shrestha A, Soriano SM, Song M, Chihara S. Intravenous colistin-induced acute respiratory failure: A case report and a review of literature. *Int J Crit Illn Inj Sci.* 2014;4(3):266-270. doi:10.4103/2229-5151.141487.
3. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care.* 2006;10(1):1-13. doi:10.1186/cc3995.
4. Spapen, Hebert D.; Jacobs R.; Van Gorp, V.; Troubleyn, J.; Honoré PM. Renal and neurological side effects of colistin in critically ill patients. *Ann Intensive Care.* 2011;1(14):1-7.
5. Sodhi K, Kohli R, Kaur B, Garg S, Shrivastava A, Kumar M. Convulsions in a critically ill patient on hemodialysis: Possible role of low dose colistin. *J Anaesthesiol Clin Pharmacol.* 2014;30(3):415. doi:10.4103/0970-9185.137282.
6. Falagas ME, Kasiakou SK, Tsiodras S, Michalopoulos A. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: A review of the recent literature. *Clin Med Res.* 2006;4(2):138-146. doi:10.3121/cmr.4.2.138.
7. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: Management considerations. *Br J Clin Pharmacol.* 2011;72(3):381-393. doi:10.1111/j.1365-2125.2011.03991.x.
8. Wallace SJ, Li J, Nation RL, et al. Subacute toxicity of colistin methanesulfonate in rats: Comparison of various intravenous dosage regimens. *Antimicrob Agents Chemother.* 2008;52(3):1159-1161. doi:10.1128/AAC.01101-07.
9. Dai C, Li J, Lin W, et al. Electrophysiology and ultrastructural changes in mouse sciatic nerve associated with colistin sulfate exposure. *Toxicol Mech Methods.* 2012;22(8):592-596. doi:10.3109/15376516.2012.704956.
10. Landman D, Georgescu C, Martin DA, Quale J. Polymyxins revisited. *Clin Microbiol Rev.* 2008;21(3):449-465. doi:10.1128/CMR.00006-08.
11. Radhakrishnan RC, Jacob S, Pathak HR, Tamilarasi V. Colistin induced neurotoxicity in a patient with end stage kidney disease and recovery with conventional hemodialysis. *Open Urol Nephrol J.* 2015;8:53-55. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L605250764%0Ahttp://rd8hp6du2b.search.serialssolutions.com?sid=EMBASE&issn=1874303X&id=doi:&title=Colistin+induced+neurotoxicity+in+a+patient+with+end+stage+kidney+disease+and+recov>.
12. Kallel H, Hergafi L, Bahloul M, et al. Safety and efficacy of colistin compared with imipenem in the treatment of ventilator-associated pneumonia: a matched case-control study. *Intensive Care Med.* 2007;33(7):1162-1167. doi:10.1007/s00134-007-0675-2.
13. Bergen PJ, Li J, Nation RL, Turnidge JD, Coulthard K, Milne RW. Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: Studies with *Pseudomonas aeruginosa* in an in vitro pharmacodynamic model. *J Antimicrob Chemother.* 2008;61(3):636-642. doi:10.1093/jac/dkm511.
14. Thein Myint, MBBS, Martin E. Evans, Donna R. Burgess and RNG. Respiratory Muscle Paralysis Associated With Colistin, Polymyxin B, and Muscle Relaxants Drugs. *J Investig Med High Impact Case Rep.* 2016;4(1).
15. Wahby K, Chopra T, Chandrasekar P. Intravenous and inhalational colistin-induced respiratory failure. *Clin Infect Dis.* 2010;50(6):e38-e40. doi:10.1086/650582.

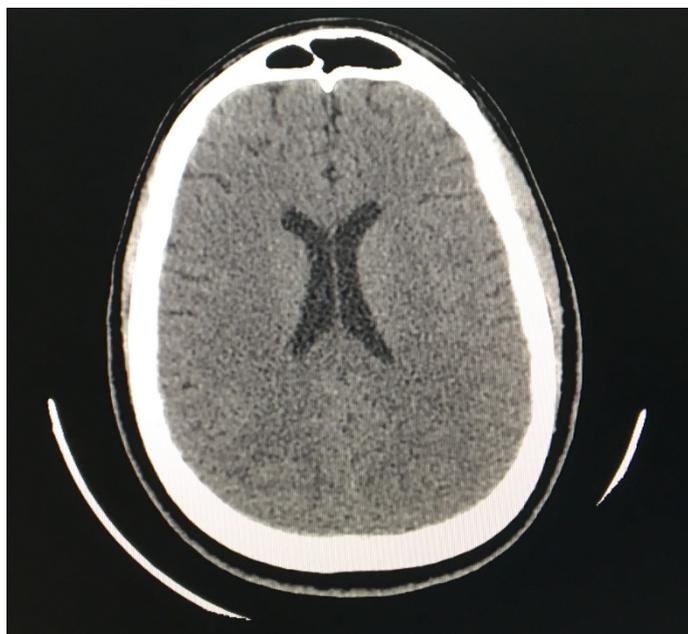


Figure 1: Skull tomography performed to rule out stroke.

Table 1: Neurological symptoms induced by Colistin and treatment

Author/Year	Number of patients	Neurologic Symptoms	Treatment
Wadia S, Tran B, 2014 ¹	1	Respiratory apnoea, neuromuscular blockade, severe comatose encephalopathy, lack of brainstem reflexes	Discontinuation of Colistin
Sodhi K et al, 2014 ⁵	1	Abnormal facial twitchings, which were mainly circumoral and initially limited to the neck, generalized tonic clonic seizures	Discontinuation of Colistin and antiepileptics drugs
Radhakrishnan RC et al, 2015 ¹¹	1	Generalized itching and tingling sensation over fingers and toes with no skin rashes or erythema, weakness and sluggish deep tendon reflexes in all limbs	Discontinuation of Colistin and urgent hemodialysis
Shrestha A et al, 2014 ²	1	Respiratory muscular weakness and acute respiratory failure	Discontinuation of Colistin
Spapen HD et al, 2011 ⁴	1	Generalized convulsions rapidly followed by acute respiratory muscle weakness and apnoea	Discontinuation of Colistin and Continuous venovenous haemofiltration
Whaby K et al, 2010 ¹⁵	1	Rapidly progressive weakness, dyspnea, severe lower extremity pain, respiratory muscular weakness and acute respiratory failure	Discontinuation of Colistin
Kallel H et al, 2007 ¹²	1	Diffuse muscular weakness	Discontinuation of Colistin