

Colistin Induced Neurotoxicity in a Patient with End Stage Kidney Disease and Recovery with Conventional Hemodialysis

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Abstract: Colistin is widely used in the treatment of multidrug resistant bacterial infections. Nephrotoxicity and neurotoxicity are risks associated with colistin use. We report the case of a 50 year old lady with end stage renal disease, treated with colistin for catheter related blood stream infection and developed muscle weakness and parasthesia. Concomitant use of meropenem may have precipitated neurotoxicity of colistin. Conventional hemodialysis was effective in reversing her signs and symptoms. Clinicians should be aware of the risk of neurotoxicity while using colistin, especially after a loading dose in patients with renal impairment. According to our knowledge, this is the first report of conventional hemodialysis reversing the neurotoxic effects of colistin.

Keywords: Colistin, end stage kidney disease, hemodialysis, neurotoxicity, side effects.

BACKGROUND

Colistin has made resurgence recently due to emergence of multi drug resistant (MDR) gram negative bacterial pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. Colistin initially went out of favor because of nephrotoxicity and neurotoxicity. Recent experience has shown that these side effects are neither common nor severe as once thought and, it has gained widespread use for the treatment of MDR gram negative infections. Colistin-induced neurotoxicity is reported but the treatment is not clear. Here, we report the case of a 50 year old lady with end stage kidney disease (ESRD) treated with colistin for catheter related blood stream infection (CRBSI) and developed neurotoxicity. Hemodialysis was successful in reversing her signs and symptoms.

CASE PRESENTATION

A 48 year old lady was on maintenance hemodialysis for two months using a temporary right internal jugular catheter presented with fever and hypotension, shortly after a dialysis session. There was no prior history of fever or any other localizing signs for fever.

She was diagnosed two months earlier to have nephrolithiasis with obstructive nephropathy and had a Double-J ureteric stent inserted for obstructed right ureteric calculus. She underwent percutaneous nephrostomy (PCN) tube drainage as the stent was blocked 8 days later. She was admitted to the intensive care unit (ICU). Investigations revealed normocytic normochromic anemia. The white blood

count (WBC) count was 3800/cu.mm with neutrophilia and toxic granules and elevated serum procalcitonin at 22.95 ng/ml. Paired blood cultures were sent from a peripheral vein and the internal jugular venous line. The right jugular catheter was immediately removed as it was deemed to be the source of infection and patient was started on empirical Piperacillin-Tazobactam. Over the next two days, the WBC increased to 34100/cu.mm with neutrophilia and increase in procalcitonin to 322.3 ng/ml. Both blood cultures were positive for multi drug resistant (MDR) non-fermenting gram negative bacteria sensitive to colistin. Antibiotic was changed to Colistin (sodium colistimethate), given at a loading dose of 6 million units followed by 2 million units once daily, and meropenem 500 mg twice daily for synergistic effect with colistin. She improved over the next 2 days as evidenced by stabilization of blood pressure and decrease in procalcitonin and WBC counts.

On the third day after initiating colistin, she complained of generalized itching and tingling sensation over fingers and toes. No skin rashes or erythema were noticed. Colistin associated neurotoxicity was suspected and its dose reduced to 1 million units per day. The following day she developed weakness of all four limbs and neurological examination showed grade 3 power in bilateral hip, knee and ankle joint flexors and extensors, right shoulder abductors, elbow flexors and extensors and grade 4 power in left upper limb muscles. No sensory deficits were elicited. Plantar reflexes were bilaterally flexor with sluggish deep tendon reflexes in both upper and lower limbs. There was no respiratory muscle or cranial nerve involvement.

There were no other metabolic causes to explain muscle weakness (S. Potassium – 4.2 mEq/L, S. Magnesium – 1.95 mg%, S. calcium-9.0 mg%, S. Phosphorous-3.6 mg%, TSH-2.5 μ IU/ml, Parathormone-234 pg/ml, urea – 89 mg%). Pruritis was considered unlikely to be due to uremia because of its acute onset and relatively low urea levels. There were

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no other skin lesions to explain pruritis. She was on amlodipine, pantoprazole, ondansetron and paracetamol which were non contributory to signs and symptoms. The Naranjo score was 7, classifying the association of ADR secondary to Colistin as probable.

Colistin induced neurotoxicity was diagnosed and Colistin was stopped. She underwent urgent hemodialysis with standard prescription for four hours. She improved after stopping the drug and a single session of hemodialysis, with return to normal muscle power within 24 hours. The paraesthesia recovered spontaneously a day later. Electroneuromyogram (ENMG) done 36 hours after dialysis showed normal nerve conduction velocities and electromyogram of upper and lower limbs, thus confirming good recovery. She was started on Levofloxacin after resolution of muscle weakness and discharged.

DISCUSSION

Colistin is a polymyxin antibiotic which binds to lipopolysaccharides and phospholipids of gram negative bacterial cell membranes, thus causing its solubilization, leakage of intracellular contents and bacterial death. It is administered parentally as a prodrug colistimethate sulfonate (CMS). Colistin has been associated with severe neuromuscular toxicity including life threatening apnoea [1]. In 1970, Koch-Weser *et al.* reported that manifestations of colistin neurotoxicity developed during 7.3% of utilizations with respiratory insufficiency and apnea seen in 2.1% of patients [2]. Neurons with high lipid content are particularly affected, leading to manifestations like peripheral and orofacial paresthesias, visual disturbances, vertigo, mental confusion, ataxia and seizures. The exact mechanism of toxicity is not known but is attributed to a presynaptic action of polymyxins that interferes with the receptor site and blocks the release of acetylcholine to the synaptic gap [3]. Presence of renal dysfunction, female sex and concomitant use of muscle relaxants, narcotics, sedatives, anesthetic drugs and steroids are potential precipitating factors for neurotoxicity [4]. Current studies have shown lower incidence of colistin induced neuromuscular toxic events. In a retrospective study including 115 patients receiving colistin, only four patients (3.5%) had neurotoxicity [5]. They also report toxicity only with prolonged treatment. Falagas *et al.* reported four patients who experienced polyneuropathy and/or myopathy during prolonged colistin therapy and concluded that colistin therapy was probably associated with the development of neurotoxicity only in one of the four patients. Even in that patient, colistin was continued for a total of 35 days and neuropathy improved gradually after the end of treatment [6]. Our patient developed neurotoxicity after three doses of colistin (cumulative dose of 10 million units) as manifested by tingling and generalized pruritis which progressed to neuropathic weakness of limbs requiring immediate stoppage of the drug. To the best of our knowledge, pruritis as a manifestation of colistin neurotoxicity has not been reported before. The fact that she had end stage renal disease and that a loading dose was given could have contributed to the early and more serious manifestations.

It can be argued that the initial loading dose of colistin is the major driver for neurotoxicity in our case. Pharmacokinetic studies on dosing of colistinmethanesulfonate (CMS) indicated that a loading dose would be beneficial since colistin has a long half-life, resulting in insufficient concentrations for the first 12 to 48 h after initiation of treatment. A loading dose of 6-9 million units was successfully administered to critically ill patients, and its potential value for fast bacterial eradication was illustrated by Mohamed *et al.* [7]. The use of loading dose is also recommended in renal impairment [8, 9]. 2 million units of colistin is recommended daily in patients with creatinine clearance <10 ml/min [9]. Our case demonstrates that even recommended doses can lead to severe neurotoxicity in patients with renal failure, especially in females.

We used colistin in combination with meropenem in order to improve its antibacterial activity, as the combination is shown to have synergistic effect in in-vitro studies. Although meropenem has very low neurotoxic potential, its concomitant use with colistin may have elicited colistin-neurotoxicity [10]. Though the traditional practice is to combine colistin with meropenem, rifampicin or other beta lactams, there is scarce data concerning the comparative effectiveness and toxicity of colistin monotherapy vs colistin-β-lactam combination therapy in patients other than those with cystic fibrosis. In a retrospective study involving fourteen patients who received intravenous colistin monotherapy and 57 who received colistin-meropenem, it was found that the effectiveness of colistin monotherapy did not appear to be inferior to that of colistin-meropenem combination therapy in MDR infections [11]. Carbapenem-induced neuromuscular blockade has never been described. Spapen *et al.* reported a patient who developed convulsions rapidly followed by acute respiratory muscle weakness and apnoea during treatment with colistin and meropenem. Considering meropenem has contributed to neurotoxicity of colistin, there is a strong need for colistin monotherapy studies in MDR infections.

The rapid progression of signs and symptoms and involvement of motor nerves compelled us to remove the drug from the body before respiratory muscle paralysis set in. Successful removal of colistin by hemadsorption with continuous venovenous hemofiltration (CVVH) at a dose of 35 mL/kg/hour has been tried in one patient earlier [12]. As our patient was hemodynamically stable, she underwent conventional hemodialysis using standard prescription of four hours duration. It was earlier reported by Marchand *et al.* that Intermittent hemodialysis (IHD) rapidly removed "normal" colistin levels of around 2 µg/mL [13]. However, no data exist on the ability of IHD to efficiently remove potentially severe toxic levels of colistin exceeding 8 µg/mL. We could not measure colistin levels in our patient nor an ENMG was done prior to dialysis but she had a rapid clinical response with abatement of signs and symptoms after hemodialysis. There was an immediate response in terms of motor improvement. Subjective sensory symptoms subsided within the next 24 hours. An electroneuromyogram done after hemodialysis was also normal. The favorable response to conventional hemodialysis in this patient is an encouraging sign as it is widely available compared to hemadsorption and CVVH.

CONCLUSION

Colistin is extensively used due to serious MDR infections. Although generally safe, loading dose of colistin recommended in critically ill patients might lead to serious neurotoxicity, especially in patients with severe renal impairment. Further studies are needed to elucidate whether this is potentiated by concomitant use of carbapenems and if so, whether colistin should be used as monotherapy. Clinicians must be aware of adverse effects of neurotoxicity while using colistin. It is encouraging to note that conventional hemodialysis may help in reversing the effects rapidly.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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