CASE REPORT

Colistin-mediated neurotoxicity

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SUMMARY

We describe a 51-year-old man who developed renal and neural toxicity after the administration of colistin. He developed respiratory apnoea, neuromuscular blockade and severe comatose encephalopathy with the lack of brainstem reflexes. After discontinuation of the antibiotic, he made a prompt recovery to his baseline neurological function. The case illustrates the importance of recognising the toxicities associated with colistin. Although recent literature details its nephrotoxicity, current data have been discordant with the rare cases of respiratory apnoea or neuromuscular blockade once cited over 30 years ago. Additionally, no cases have ever described the profound encephalopathy with lack of brainstem function described here. The awareness of colistin's potentially fatal effects must be kept in mind when administering this antibiotic. Vigilance of the encephalopathic picture can also facilitate the diagnosis of colistin-mediated neurotoxicity in a patient with altered mental status of otherwise unknown aetiology.

BACKGROUND

The use of polymyxin antibiotics, such as colistin, declined in the late 1960s due to adverse toxicities. However, efficacy against multidrug resistant Gram-negative organisms (commonly seen in healthcare-associated infections) has garnered new attention in this old antimicrobial class.¹

Recent reports on colistin detail its renal toxicity, but far less data estimates its neural toxicity. Commonly reported neurotoxic effects include benign peripheral paresthesias, changes in vision, vertigo and ataxia. No cases of respiratory apnoea or neuromuscular blockade have been reported in over 30 years.^{1 2} We present a case of profound encephalopathy, neuromuscular blockade and respiratory apnoea from the administration of colistin.

CASE PRESENTATION

The patient is a 51-year-old man with a history of diabetes and paraplegia being treated in the intensive care unit for multidrug resistant ventilator-associated pneumonia after sputum cultures grew Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii* and extended-spectrum β -lactamases *Proteus mirabilis*. He was started on the following antibiotics: doripenem 500 mg intravenously three times a day, colistin 275 mg intravenously two times a day and tigecycline 50 mg intravenously two times a day. On the seventh day of antibiotics, he was awake and responsive, interacting appropriately, and moving upper extremities. By the eighth day of antibiotics, he was unarousable. On examination, he was breathing at the ventilator set rate of 14 (previously breathing above the ventilator at a rate of 20). His

neurological examination demonstrated a comatose level of alertness. He lacked all cranial reflexes. Motor examination showed 0/5 strength in all extremities, sensory examination lacked response to painful stimuli, and no reflexes were elicited.

INVESTIGATIONS

Laboratory studies demonstrated creatinine elevation of 1.73, above baseline of 0.70. The remainder of the patient's chemistry panel was within normal limits. Urinalysis demonstrated moderate blood, protein and granular casts. CT of the brain was normal. EEG revealed attenuation of background activity and generalised slow waves, consistent with a severe encephalopathy.

DIFFERENTIAL DIAGNOSIS

- Anoxic brain injury
- Toxic metabolic derangement (such as adrenal insufficiency, medication toxicity, etc)
- Meningitis

TREATMENT

Colistin toxicity was diagnosed and the patient's antibiotics were discontinued. His renal function and neurological status began to show slow improvement 48 h after discontinuation of colistin. By 72 h, he had complete recovery of neurological function (moving upper extremities, conversing, alert and oriented), although he had no recollection of the encephalopathic episode. Nevertheless, once his mental status recovered, no residual neurological effects were noted.

DISCUSSION

The purpose of our case report is to describe the profound toxicity associated with colistin. Colistin is administered as an inactive prodrug. About 60% of the inactive form is renally excreted unchanged in the first 24 h.³ Based on the patient's weight, he received 4.6 mg/kg/day, less than the recommended maximum 5 mg/kg/day. He suffered colistin-induced acute tubular necrosis evidenced by the creatinine elevation and the urinalysis findings. The subsequent decrease in renal excretion of the inactive prodrug led to higher conversion and accumulation of active form, causing a toxic cycle. Our patient's severe neurological decline was unique in that he was severely encephalopathic and he lacked complete brainstem, sensory and motor reflexes. These reactions have not been described in previous literature. Moreover, he developed respiratory apnoea as evidenced by ventilator-dependent breathing. His prompt recovery after discontinuation of colistin underscores the importance of monitoring respiratory function in patients with suspected colistin

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Learning points

- ▶ Colistin toxicity is a rare but potentially fatal effect of the drug. Although benign neuropathic reactions have been described, recognition of the more severe respiratory apnoea, neuromuscular blockade and severe encephalopathy can aid in the diagnosis of colistin-mediated neurotoxicity in a patient with altered mental status of unknown aetiology.
- ▶ Caution should be exercised when using colistin in patients with acute or chronic renal disease, as it can significantly increase toxic levels of the active metabolite. More studies are still needed to guide optimal dosing of colistin, particularly in patients with renal disease.
- ▶ Recognition of colistin-mediated neurotoxicity can aid in the acute and long-term treatment of patients. Patients with suspected toxicity may need intubation to protect against respiratory apnoea.
- ▶ Prognosis of adverse colistin toxicity is generally good once the offending agent is discontinued. If neurotoxicity is suspected, recovery may take up to 72 h.

toxicity, particularly in patients with renal disease. The case also suggests that colistin should be stopped in patients who develop an acute change in renal function, as it can hasten and herald the potentially fatal neurotoxic effects.

Studies are needed to clarify the optimal dosing of colistin. Prior cases have documented improvement in colistin-mediated neuromuscular blockade with the use of edrophonium⁴ but further studies are needed to determine the role of anticholinesterase inhibitors in the treatment of neuromuscular blockade or respiratory apnoea seen with colistin toxicity.

Competing interests None.

Patient consent Obtained.

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