COLISTIN-INDUCED NEPHROTOXICITY: A CASE REPORT

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ABSTRACT
Colistin, also known as Polymyxin E, re-introduced into clinical practice due to emergence of resistance of gram negative pathogens to existing therapeutic options. But its adverse effects such as nephrotoxicity and neurotoxicity still remain an inevitable issue. This is a case report of colistin induced nephrotoxicity happened in an young male patient with aplastic anemia. Factors that influence the risk of colistin nephrotoxicity are age, dose and duration of therapy. Maintenance doses of colistin require adjustment according to renal function because even at a specific creatinine clearance there is very large interpatient variability in the plasma colistin concentration and this makes colistin dose selection difficult. Therapeutic drug monitoring of polymyxins is needed as it can assist in optimising dose regimens and minimise the development of polymyxin-induced nephrotoxic effects.

KEYWORDS: Colistin, also known as Polymyxin polymyxin-induced nephrotoxic effects.

INTRODUCTION
Colistin (polymyxin E), developed 60 years ago marked as a sporadic use during the period of 1980-2000 owing to the reported high risk of nephrotoxicity. The mechanism of which was not known, but it was hypothesized that colistimethate sodium (CMS) induces membrane permeability which in turn causes an influx of cations, anions and water resulting in cell lysis. Colistin was reintroduced for the management of gram negative Pseudomonas aeruginosa and Acinetobacter baumanii recently as a consequence of necessity. It was in Japan 1947, colistin was first isolated and used until 1980s for the treatment of gram negative bacilli infections. Colistin is a non-ribosomal cationic polypeptide bactericidal antibiotic isolated...
from Bacillus polymyxa. Its mechanism of action is now generally agreed as colistin binds to lipid A of the lipopolysaccharide molecules of the outer membrane of gram-negative bacteria and displaces calcium and magnesium from the phosphate groups of the lipopolysaccharides. Hence the stability is lost and results in the leakage of cytoplasmic material, ultimately leading bacterial cell lysis and death.[1-5]

Polymyxins were made fall out of use in 1980s due to their adverse effects, including nephrotoxicity and neurotoxicity. But later in 1990s they were re-introduced in clinical practice because of the emergence of resistance of gram negative pathogens to ongoing antimicrobials. Both neurotoxicity and nephrotoxicity of polymyxins are reversible if discontinued early. Close monitoring of renal function and avoidance of co-administered nephrotoxic medications will help to an extent.[6]

SIGNIFICANCE OF THE CASE
A significant change in creatinine level in patients receiving CMS treatment was observed in the first month after the initiation of therapy. Some reports demonstrates a 4-fold increased risk of nephrotoxicity in patients receiving CMS for >14 days, manifesting a relation of toxicity and the total dose and duration of therapy. Contrary to this other studies indicate that nephrotoxicity is not associated with the dose per day (mg/kg/day), but with the total cumulative dose.[7]

CASE DESCRIPTION
A 26 years old aplastic anaemic male patient was admitted to bone marrow transplantation unit with severe headache and febrile neutropenia. Initial investigation revealed E.Coli bacteremia, large intracranial bleed and grade I medical renal disease. He was started on multiple iv antibiotics including colistin 3.5 million units TID and received frequent platelet transfusions. On the 6th day of colistin therapy, serum creatinine was observed to be 3.1mg/dl where the baseline level was 0.9mg/dl. Other causes of acute kidney injury such as, shock, renal artery stenosis, glomerulonephritis, mechanical obstruction etc were ruled out. The dose and frequency of colistin was reduced from 3.5 MU TID to 2 MU OD on the 11th day of colistin therapy. Serum creatinine came down to 2.5mg/dl within 48 hours. Hence colistin was increased to 2 MU BD and no further elevation of creatinine levels was seen.
DISCUSSION

A systematic review was conducted by Falagas et.al from 1950 to 2005 and they found rates of colistin associated nephrotoxicity from 0% to 50.0%.[8] Recent literatures also show similar rates, 10.0% to 45.0%. [9-11] Colistin is commercially available as colistimethate sodium (CMS). Colistin is a prodrug and it must be converted to pharmacologically active moiety to be effective. Only small fraction of the dose (20-25%) is converted to its active form in patients with good renal function while most of the colistimethate dose is renally excreted.[12] Although minimally excreted, urine contains therapeutic concentrations of colistin as highly excreted colistimethate undergoing conversion to colistin in the urinary tract itself.[13]

Factors that influence the risk of colistin nephrotoxicity are age, dose and duration of therapy. Our report shows that when the dose of colistin was reduced from 3.5 million units TID to 2 million units OD elevation of serum creatinine began to cease. Studies conducted in United States reported greater than 40% nephrotoxicity when higher dose was used whereas studies outside United States observed less than 20% nephrotoxicity when they used lower doses of colistimethate.[14]

Maintenance doses of colistin require adjustment according to renal function because even at a specific creatinine clearance there is very large interpatient variability in the plasma colistin concentration. This makes colistin dose selection difficult.[12] Therapeutic drug monitoring of
polymyxins is needed as it can assist in optimising dose regimens in individual patients, minimise the emergence of resistance and development of polymyxin-induced nephrotoxic effects. Polymyxin causes morphological changes in mitochondria and membrane potential as well as apoptosis of tubular cells of kidney.\[^{15}\]\ One of the major dose-limiting adverse effect of colistin is nephrotoxicity. Management strategies like decreasing the daily dose of colistimethate in patients with declining kidney function can restore desired steady-state concentration of colistin.

Renal function has to be monitored when colistin is prescribed. Sepsis may potentiate colistin effects on kidney. A current article shows 2.5 to 7 fold higher incidence of nephrotoxicity in people with baseline renal dysfunction than with healthy people.\[^{16}\]\ Withdrawal of colistin, even in the presence of nephrotoxicity should be decided with supreme importance. In case of renal toxicity, it is advised to modify the colistin dose or frequency (or both) or resort to alternative therapy.

**CONCLUSION**

The drug colistin, being primarily excreted by the kidneys, marks nephrotoxicity as the most common adverse event. The potential for nephrotoxicity of this valuable drug could be minimized by routine assessment of serum creatinine levels, modification of colistin dose with renal function, shortening the duration of antimicrobial treatment and avoiding co administration of other nephrotoxic drugs.

**REFERENCES**

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