Review Article

Review on Effects of Colistin Induced Nephrotoxicity

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ABSTRACT

Colistin was first introduced in 1952 and was used until the early 1980s for the treatment of infections caused by Gram-negative bacilli. It is an effective antibiotic that was introduced many years ago and was withdrawn because of its nephrotoxicity. Nowadays, reemergence of colistin antibiotic for multi-drug resistant Gram-negative infections, and a new high dosing regimen recommendation increases concern about its nephrotoxicity. This review tries to give a view on colistin nephrotoxicity, its prevalence mainly in high doses, the mechanism of injury, risk factors, and prevention of this kidney injury.

Keywords: colistin, gram negative bacilli, nephrotoxicity, multi drug resistant gram negative infections.

INTRODUCTION

Colistin is a glycopeptide antibiotic which belongs to the class polymixin. Colistin is also known as polymyxin-E.[1] It was the first antibiotic with significant activity against multiresistant (MSR) pathogens such as *Pseudomonas aurginosa, Acinetobacter baumannii,* and *Klebsiella pnuemoniae*. Commercially two forms of colistins are available, they are coilstin sulphate for oral and topical use, sodium colistimethate (CMS) for parenteral and inhalation purpose. CMS is a less potent and less toxic prodrug of colistin.[2,3] Colistins are available for clinical use in 1960s but it was replaced in 1970 with other antibiotics because of its toxicity.[4] Out of this nephrotoxicity is the most common and concerning adverse effect of colistin. Clinical manifestation of colistin nephrotoxicity includes a decrease in clearance of creatinine, proteinuria and oliguria. These effects are dos dependent and most of them are reversible.[5]

METHODS

Data for this review were obtained through literature searches of publications included in PubMed from 1950 until May 2005, references cited in relevant articles, and the world-wide web. The main search terms used in searches of literature databases were 'colistin', 'polymyxin E', 'polymyxin B', 'adverse effects', 'nephrotoxicity', 'colomycin', 'colimycin', 'neurotoxicity' and 'toxicity'. Only English language papers were reviewed

DISCUSSION

Common Toxicity and Adverse Effects

Nephrotoxicity and neurotoxicity are the most common adverse effects of colistins. Neurotoxicity is dose dependent and reversible in nature.[6] Major clinical manifestations are weakness, partial deafness, difficulty in swallowing, ataxia, eyelid ptosis visual disturbances, vertigo, confusion, hallucinations, seizures, ataxia, neuromuscular blockade leading to respiratory failure , peripheral and facial paranesia.[7]

Renal toxicity mainly includes acute tubular necrosis manifested as decreased creatinine clearance and increased serum urea and creatinine levels proteinuria or oliguria. Other common side effects includes the use of colistin include hypersensitivity reactions, skin rash, urticaria, generalized itching, fever, and mild gastrointestinal disorders.[8]

Mechanism of Colistin Induced Nephrotoxicity

Nephrotoxicity is found be one of the most common toxic effects of colistin therapy because of the reason that the drug is excreted through the kidney and the elevated blood levels may impair the function of kidney. It has been found that the toxic effect of colistins may be due to the D-amino butyric acid content and fattyacid component in their structure.[9] The possible mechanism by which the colistin causes nephrotoxicity is by increasing membrane permeability, that results in an increased influx of cations, anions and water leading to cell swelling and lysis and also finally apoptosis have been implicated.[10]

Different experimental studies showed that colistin increased the transepithelial conductance of the urinary bladder epithelium.[11] The magnitude of the conductances increased was dependent on concentration and length of exposure to colistins as well as the divalent cation concentration.[23] Nephrotoxicity associated with the use of colistin is considered to be dose dependent and duration of therapy.[12]

Risk Factors

Nephrotoxicity occurs as a result of using collistimethate sodium (CMS) is less toxic as compared to the other polymixins.[13] The patients with early kidney injury had a

high mortality rate than those with late kidney injury. Patients who have undergone CMS therapy for more than 14 days are more prone to develop renal failure Children are less prone to develop colistin induced renal failure.[14,15] The other independent risk factors of colistin induced nephrotoxicity were old age , long duration of colistin therapy and high dose of intravenous administration of colistin (less than 5mg/kg/d) and concombinant use of vancomycin therapy.[16,17] Male sex , co-administration of calcine urine inhibitors, hyperalbuminemia and hyperbilirubenemia were the other risk factors which leads to colistin induced nephrotoxicity.[18]

Treatment Option for Nephrotoxicity

While observing the primary symptoms of improper kidney function, discontinue the colistin therapy as early as possible. Administration of any diuretic like mannitol has been suggested to enhance the renal clearance of the drug and thereby reduce the level of drug in the serum.[19] After detection of renal dysfunction frequent monitoring of fluid intake and output and provide suitable management to maintain fluid and electrolyte balance.[20] According to previous studies and reports suggested that haemodialysis and peritoneal dialysis decreases the serum level of colistin but now a days it is not preferred.[21] Exchange transfusions have been suggested as an effective method for the removal of colistin.[22]

Prevention

Dose adjustment, duration of therapy and oxidative damage attributed to colistin is suggested as a mechanism of nephrotoxicity.[23] Different studies carried out the comparison of colistin and colistin with N –acetyl cysteine (NAC).[24] It is found that NAC reduced renal tissue superoxide dismutase (SOD), reverse staining of inducible nitric oxide synthase(i-NOS) and nuetrophin-3 and significantly reduced immune staining of endothelial NOS. Therefore administration of colistin along with NAC probably reduces the oxidative damage to colistin.[25] Recent studies assessed administration of grape seed proanthocyanidin extract (GSPE)with colistin significantly reduced the level of blood urea nitrogen and creatinine , when compared to administration of colistin alone.[26] GSPE is a naturaly derived substance with antioxidant, antiapoptotic, anticarcinogenic, vasodilator and anti-inflammatory effect which is obtained from the black grape.[27] The mechanism involved in preventing colistin induced renal injury is an antiapoptotic effect through reducing caspase 3 level and an antinecrotic effect through reducing calpain 1 and caspase 3 level.[28,29]

CONCLUSION

Colistin is a nephrotoxic antibiotic because of the worldwide increase in nosocomial infections has lead to an increase in its usage. Nephrotoxicity is the concerning adverse effect of this drug. The mechanism of nephrotoxicity is through an increase in tubular epithelial cell membrane permeability, which results in cation, anion and water influx leading to cell swelling and cell lysis. There are also some oxidative and inflammatory pathways that appeared to be involved in colistin nephrotoxicity. Risk factors of colistin nephrotoxicity can be categorized as dose and duration of colistin therapy, co-administration of other nephrotoxic drugs, and other patient related factors such as age, sex, hypoalbuminemia, hyperbilirubinemia, underlying disease and severity of patient illness. With in these informations we cannot conclude the toxic effects of colistin.It can be suggested that, both the duration of use as well as the cumulative dose of colistin should be taken into account when predicting colistin nephrotoxicity. Also it can be suggested that colistin should be used carefully administerd in older patients, patients using concurrent mediations, and patients with high blood urea levels. In addition, all patients should be closely monitored for renal nephrotoxicity. Significantly nephrotoxity can be reduced with the oral administration of 100 mg/kg from the first day of colistin use and it reduced the nephrotoxity effect by reducing oxidative damage, caspase-mediated apoptosis, and caspase 1 and calpain 1 levels.

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