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Review Article

Polymyxins leading to nephrotoxicity

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ABSTRACT

Drug resistance gram-negative bacteria are the most hazardous type of germ because they cause life-threatening illnesses. Polymyxins are cyclic lipodecapeptide antibiotics that are effective against gram-negative bacteria like *Acinetobacter*, *Pseudomonas*, and other *Enterobacteriaceae* (such *Klebsiella*, *Escherichia coli*, and *Serratia*). Polymyxins kill bacteria by rupturing the bacterial outer membrane (OM). The main side effect of this antibiotic class is the development of kidney damage. Transposable genetic elements, such as MCR genes, can encode bacterial resistance to polymyxins. Colistin's prodrug is colistimethate sodium (CMS). Polymyxin dosage should be modified based on renal function. Polymyxins have demonstrated excellent clinical results, which have aided in the development of a better dosage regimen. Monte Carlo simulations were used to determine the most effective polymyxin dosages. Polymyxin resurgence has resulted in the eradication of multidrug resistant gram negative bacteria.

Keywords: Gram-negative, Polymyxins, Colistimethate sodium, MCR genes, Monte Carlo simulations, Dosing

INTRODUCTION

In order to address the global rise in antimicrobial drug resistance, particularly resistance to carbapenems and third generation cephalosporins, the WHO produced an R and D list relevant to antibiotic-resistant bacteria and the steps needed.

Multidrug resistant gram-negative bacteria, such as *Acinetobacter, Pseudomonas*, and different *Enterobacteriaceae* (including *Klebsiella*, *Escherichia coli*, and *Serratia*), are the most dangerous group of germs because they can cause extremely dangerous infections *(bacteremia* and *pneumonia*).[1]

The medical community now understands how crucial it is to tackle bacterial resistance, which has resulted in the resurgence of once-disfavored antibiotics like the cyclic peptide Polymyxin B and its relatives.[2]

METHODS

Polymyxins

Structure, function and consequences

Due to their five free amino groups, polymyxins [polymyxin B (PMB)] and polymyxin E (colistin) are cyclic lipodecapeptide antibiotics that are particularly efficient against Gram-negative bacteria like the majority of *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aureginosa*. Each polymyxin member has a cyclic heptapeptide core that is connected to a linear tripeptide 'panhandle' that has an N-terminal fatty acyl moiety.[3]

An N-terminal fatty acid side chain is joined to a poly-cationic deca-peptide backbone to form the structure of polymyxins. Many cationic antimicrobial peptides (CAPs)

have amphipathicity, which is conferred by these structural characteristics.[4] The revival of antiquated antibiotics like polymyxins as a last-resort treatment for diseases brought on by MDR (multidrug resistant) bacteria. Gram-negative infections that are resistant to every other antibiotic that is currently on the market.[5]

Nephrotoxicity is one of this antibiotic class's main side effects. Only polymyxins B and E are being applied in clinical settings. Colistin, also known as polymyxin E, is a substance that is frequently used and studied and is used to lessen nephrotoxicity in the form of colistimethate sodium. The main problem restricting the use of this class of antibiotics is the development of renal damage, particularly acute renal failure (ARF).[6]

Although the efficacy of polymyxins against the majority of gram-negative bacteria, such as *Pseudomonas aureginosa* and *Acinetobacter baumanni*, has not been called into question, early administration of polymyxins was linked to reports of unfavourable renal and neurological effects in a sizeable number of patients. Thus, as newer antibiotics with the same or broader antibacterial spectra and reportedly lower toxicity were introduced, compounds from this class of antibiotics were gradually phased out of clinical use, with the exception of cystic fibrosis patients who experience recurrent pulmonary infections brought on by multidrug-resistant bacteria.[7] Therefore, it's important to utilise the polymyxins, our last resort antibiotics, carefully to avoid the development of resistance. Recent research employing polymyxin has produced encouraging clinical outcomes that have helped in developing a better dose regimen.[8]

The primary mechanism by which polymyxins exert their antibacterial activity is by attaching to lipopolysaccharides (LPS) and rupturing the bacterial outer membrane (OM). For the explanation of the mechanism and rational medication design, it is crucial to comprehend how polymyxins and the OM interact.[9] Due to its higher PK properties and lower risk of nephrotoxicity, polymyxin B was recommended as the preferred drug above colistin.[10] Recent literature has suggested, among other things, ways to improve dose, substitute administration techniques, and other synergistic antimicrobial combinations to increase the potency of polymyxins.[11] Bacterial resistance to polymyxins can be encoded via transposable genetic elements, such as mcr genes, or it can be chromosomal and linked to the alteration of LPS.[12] However, a new plasmid-mediated transferable resistance determinant, the MCR-1 (mobile colistin resistance) gene, encoding a phosphoethanolamine transferase, has recently been described and the MCR-1 genewas initially discovered in *Enterobacteriaceae* (*E. coli*). Acquired resistance to polymyxins is typically associated with chromosomal mutations.[13] The *S. typhimurium* isolate's MCR-1 geneis found on an IncHI2-plasmid, as opposed to the Incl2-like plasmids found in the isolates of E. coli from Asia.In the clinical situation, the MCR-1 genemay significantly increase morbidity and mortality linked to colistin failure.[14] Concerningly, the acquisition of the MCR-1 gene by readily conjugative, multidrug-resistant IncHI2 plasmids, as a variety of antimicrobials other than polymyxins may now make co-selection of mcr-1-positive isolates easier.[15] MCR-1 gene input lowers resistance to hydrophobic antibiotics while altering membrane permeability and protecting the host against colistin. Therefore, MCR-1 is found at the membrane, and its expression has an impact on both cellular and colony shape.[16]

Toxicity of polymyxines

It was evident from a number of studies published in the 1960s and 1970s that parenteral administration of polymyxin was strongly linked to significant nephrotoxicity. The frequency of nephrotoxicity was, however, less frequent and less severe than those described 40 years ago, according to published experiences of systematic polymyxin usage after their recent resurgence.[17] The central nervous system and the renal system are both affected by polymyxin toxicity. Polymyxins' amphipathic character, which would permit entry into lipid-rich nerve cells, may help to explain their neurotoxicity. Presynaptically acting polymyxin B competitively inhibits the neurotransmitter acetylcholine, and the intracellular calcium depletion that results may cause a protracted depolarization.[18]

It is believed that the direct interaction between PMB and neurons, which results in dose-dependent neurotoxicity, is what causes polymyxin B neurotoxicity. PMB may prolong depolarization, deplete calcium, and trigger histamine release in addition to inhibiting acetylcholine's activity at the neuromuscular junction.[19] Reduction in viability, an increase in apoptosis, and the release of the lactate dehydrogenase enzyme, which signals cell death by necrosis, were used to measure the cytotoxicity of PMB. The administration of PMB entails steps to reduce side effects, with nephrotoxicity serving as the primary focus to identify hazards and the mechanism of renal protection.[20]

The idea that oxidative stress and mitochondrial dysfunction play a significant role in polymyxin-induced nerve injury is being supported by a growing body of research in recent years. Colistin-induced neuronal cell death also involves the P53, PI3k/Akt, and MAPK pathways.[21] The adverse effect of colistin that is more prevalent and serious is nephrotoxicity. Reduced creatinine clearance, proteinuria, cylindruria, or oliguria are some of the clinical signs of colistin nephrotoxicity. A less toxic and potent prodrug of colistin is called CMS.[22] Colistimethate sodium causes kidney damage by building up in proximal tubule cells proving that megalin, a 600 kDa glycoprotein produced in the apical membrane of the proximal tubule, binds to these cells' ability to reabsorb CMS. When colistin was given along with a megalin-releasing agent (maleic acid) and megalin ligands (cytochrome C and FRALB), biological models

demonstrated a decrease in renal accumulation and a concurrent increase in urinary excretion of colistin.[23]

Nonapeptides having an N-terminal amine moiety of a certain regio-and stereochemistry have more in vitro activity and less cytotoxicity than polymyxin B. A promising combination of low cytotoxicity and kidney exposure, which results in low toxicity, is provided by compounds with a beta-branched aminobutyrate N-terminus with an aryl group.[24]

Treatment through polymyxins

We use polymyxin B should not exceed 200 mg/day if the patient has carbapenem resistant bacteria, CRD infection, or gram-negative bacteria with inadequate antibiotic treatment. This helps to minimise side effects and boost patient compliance.[25] The two clinically utilised polymyxins, colistin and polymyxin B, have similar in vitro activities but differ significantly in the time course of concentrations reached in the hours and perhaps days after therapy begins due to different given forms.[26] Colistin is typically used for urinary tract infections brought on by MDR gram-negative bacteria, whereas polymyxin B is typically prescribed for bloodstream infections.[27]

The excess reaction rate in heavier individuals may be avoided with a colistin dosage proportionate to the square root of the patient weight, while producing more effective blood levels in light patients.[28] According to the current agreement, polymyxin B dosages should be based on body weight (2.0-2.5 mg/kg as a loading dose, followed by 1.25-1.5 mg/kg every 12 hours) and adjusted in accordance with renal function.[29]

These medications' therapeutic usefulness will likely be extended with effective and prudent use. It is hoped that polymyxins will act as a stopgap until new and effective treatments are created.[30] Several approaches have been put forth to reduce polymyxin-inducing toxicities in order to preserve the clinical utility of this last-resort class of antibiotics. These include therapeutic drug monitoring, customised dosing with adaptive feedback control, and avoiding the simultaneous administration of toxic drugs.[31]

Combination therapy of polymyxins

Combining polymyxins and the FDA-approved natural substance curcumin had a synergistic inhibitory effect on bacterial growth. The ability of polymyxin to permeabilize the outer membrane may be the cause of the synergistic impact since it makes it easier for curcumin to reach its intracellular targets at higher doses.[32]

Netropsin, a pyrrole-amide anticancer medication, influences DNA's positive supercoiling and raises the average twist per base, but it has no effect on the DNA's *in vitro* contour length. When combined with polymyxin B, netropsin uptake through the outer membrane is enhanced, boosting netropsin binding to bacterial DNA and reducing cell growth. Netropsin alone does not appreciably suppress bacterial growth.[33]

Dosing regimen of polymyxins

The method of drug delivery selected to achieve the therapeutic goal is the dose regimen. This is dependent on the medication being used, the illness being treated, and the characteristics of the patient.

The aforementioned attending medical teams had complete discretion over the Polymyxin B regimens (daily dose, dosing interval, duration of intravenous administration, and duration of therapy). The recommended daily dose range for polymyxin B was 1.5 to 2.5 mg/kg of real body weight.[34]

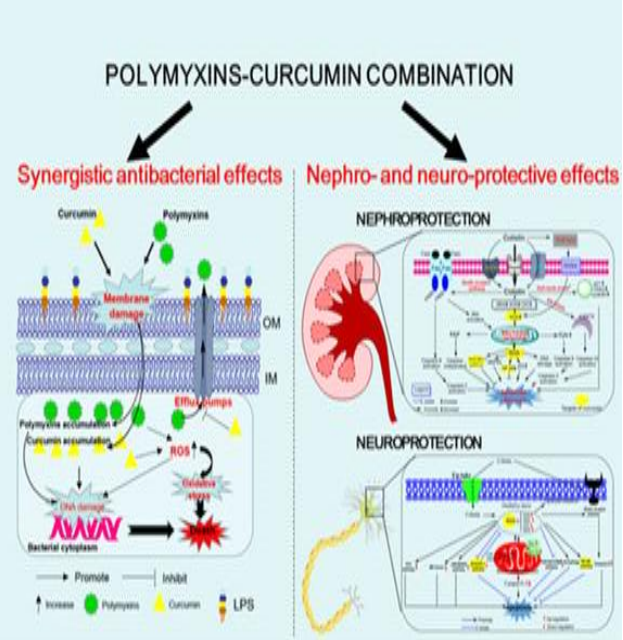

Figure 1: Polymyxins-curcumin combination.

Monte Carlo simulations of polymyxins

The probability target attainment (PTA) and cumulative proportion of response (CFR) of polymyxin B against CRE (Carbapenem-resistant *Enterobacterales*) were estimated using Monte Carlo simulations. The most effective dose of polymyxin B, 1.5 mg/kg per 12 hours, could produce the greatest CFR values (82.69%) against CRE according to the findings of Monte Carlo simulations.[35]

CONCLUSION

Polymyxins are regarded as one of the few antibiotics of last resort that are effective against Gram-negative bacteria. Colistimethate sodium is especially effective at killing sensitive strains of *Pseudomonas aureginosa*. Polymyxin antibiotics are often used as a last resort when modern antibiotics fail or are contraindicated since they are relatively neurotoxic and nephrotoxic. Polymyxins are

administered to patients in accordance with the polymyxin dosing schedule. Lowering the doses of these antibiotics can help to lessen their side effects.

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