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Polymyxin B Induced Hypotension

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Abstract

Background: Two unusual case reports of polymyxin B induced hypotension

Case summary: Polymyxins are reintroduced for the treatment of MDR gram negative organisms, although sufficient data is available regarding the nephrotoxicity and neurotoxicity of poly B very few data is available regarding the cardiovascular effects of polymyxin B.

Case 1: A 51 years old female patient diagnosed with sepsis due to cellulitis was growing multidrug resistant acinetobacter from the infected site has developed hypotension after receiving poly B.

Case 2: A 59 year old male patient who has undergone CABG had MDR Klebsiella pneumonia in the urine culture only sensitive to polymyxins, similar episodes of hypotension were suspected as the end result of poly B administration.

Conclusion: Two patients developed polymyxin induced hypotension after been exposed to intravenous polymyxin B for treating gram negative organisms.

Keywords: MDR Gram negative bacteria; Antibiotic; Polymyxin B; Clinical intervention; Hypotension

Introduction

With an increase in infectious diseases, the overall consumption of antibiotics has enormously increased. However, antibiotics are not indicated in majority cases and antibiotic utilisation is misused leading to antimicrobial resistance. Micro organisms like gram negative enterobacteriaceae has developed resistance to various antibiotics leading to decreased therapeutic options available [1]. Antibiotics like polymyxins are reintroduced for the treatment of gram negative organisms, although it has produced significant clinical outcomes [2], very limited data is available regarding the cardiovascular complications of the drug [3]. Here we report 2 cases with polymyxin induced hypotension, to the best of our knowledge we believe that it is rare and is caused due to toxicity of the drug.

Polymyxins are reintroduced as a last resort of drug with a rise in infections due to gram negative bacteria and the lack of new antibiotics to combat them [1].

These are group of polypeptides discovered from different species of *Paenibacillus polymyxa* (previously *Bacillus polymyxa*) in 1947 [2,3]. These are the bactericidal drugs that bind to the lipopolysaccharides and phospholipids of the outer cell member of gram negative bacteria. Polymyxins interact with lipopolysaccharides resulting in increased permeability of the bacterial cell member causing cytoplasmic leakage and resulting in cell death [4]. Various studies have demonstrated the mechanism of polymyxin resistance limiting the usage of the drug.

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Spectrum of activity includes various gram negative organisms including *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, *Acinetobacter* spp. *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Citrobacter* spp., *Yersinia pseudotuberculosis*, *Haemophilus influenzae*, *Pasteurella* spp., *Bordetella pertussis*, and *Legionella pneumophila*. Majority of nosocomial pathogens are susceptible [5]. Some of the organisms have acquired intrinsic resistance to polymyxins which include *Burkholderia* spp., *Proteus* spp., *Providencia* spp., *Morganella morganii*, and *Serratia* spp. Additionally, *Brucella* spp., *Neisseria* spp., and *Chromobacterium* spp. isolates are also resistant. The recommended loading dose of polymyxin B is 2.0 mg/kg-2.5 mg/kg over 1 hour infusion The maintenance dose includes 1.125 mg-1.5 mg (equivalent to 12,500 IU/kg-15,000 IU/kg of total body weight every 12 hours over 1 hour infusion [6]. Earlier findings illustrate that nephrotoxicity and neurotoxicity are the most common side effects [7], associated with polymyxin B but cardiovascular toxicity is rare to the best of our knowledge [8,9]. We report a two cases with polymyxin induced hypotension in our health care.

Case Presentation

Case 1

A 51 year old female patient was presented with the chief complaints of left lower limb swelling, fever with chills and rigors with decreased urine output. She had a past history of Osteoarthritis with B/L knee replacement therapy. Infectious disease consultation was given keeping in view of her condition she was then diagnosed with Left lower limb cellulitis. Appropriate therapeutic regimen was given along with that supportive therapy has been initiated Blood and urine culture was sent before the initiation of antibiotics and prophylactic antibiotic therapy has been started. Urine culture reported *E. Colli* sensitive to carbapenem and clindamycin. Meropenem is escalated based on the urine culture. The patient has been worsening even after the appropriate therapy. On day 5 swab and tissue culture was sent from the infected site. *Acinetobacter* was growing from the infected site sensitive to tigecycline and polymyxins. In view of deterioration, tigecycline was added. Patients developed severe shortness of breath and breathing difficulties, in view of the condition ET culture was

sent and the culture was positive with multidrug resistant *Klebsiella pneumoniae* sensitive to only polymyxin. Hence Polymyxin B 10 LU was given as loading dose and 5LU IV BD was given as maintenance dose intravenously to the patient. On day 6 we observed the persistent decrease in the fall of blood pressure following the 4th dose of administration of polymyxin B (120/80 to 90/60). We couldn't rechallenge the patient because of her worsening condition. While hypotension is usually a complication of sepsis, the details in this case suggests that the episodes of hypotension are majorly related to polymyxin B administration than an uncontrolled sepsis. The episodes of hypotension started to the hypotensive episodes the pre and post polymyxin B pressures were markedly different.

Case 2

A 59 years old male patient was admitted on 8.3.2019 with the chief complaints of shortness of breath, chest discomfort, syncope and palpitations. He had a past history of hypertension, Angina and coronary artery graft (2 months ago). The patient was advised for PTCA. On the 2nd day of admission (10.3.2019) CABG was performed by cardiology specialists and cefuroxime was given as a prophylactic antibiotic. After the surgery the patient was stable and shifted to ward. He was stable until day 5 but on day 6 (14.3.2019) the patient developed rise in temperature, diffuse abdominal pain, tremors, weakness, vomiting along with loose stools and his serum creatinine also raised with deranged LFTS. Department specific consultations were taken into consideration and USG abdomen revealed Cholelithiasis and diagnosed as acute kidney injury with probable sepsis assuming source as urinary tract infection or gallbladder .The patient was advised for blood culture, urine culture along with procalcitonin levels. On day 7 (15.3.2019) patients had fever spikes keeping in view of this meropenem was started empirically along with other supportive treatment. On day (17.3.2019) culture sensitivity report revealed *Klebsiella pneumonia* sensitive to only polymyxins, based on the urine cultures polymyxin B was escalated and meropenem was deescalated. Polymyxin was started on 17.3.2019, 20 L/U was diluted in 100 ml normal saline, infused over 45 minutes as loading dose, then 10 L/U in 50 ml normal saline infusion was given for 45 minutes, twice a day was given as maintenance dose. On the second dose of polymyxin infusion there was substantially fall in the blood pressure from 130 mmhg/80 mmhg to 110 mmhg/70 mmhg within one hour of polymyxin infusion, third dose of polymyxin i.e., on 18.3.2019 11:20 pm the blood pressure further decreased to 60 mmhg/40 mmhg. Patient was immediately shifted to intensive care unit and the episodes of hypotension were suspected as the end result of polymyxin B administration on this account polymyxin B was replaced with Inj. colistin 3MU TID and Inj. meropenem 1 gm TID. The blood pressure consistently returned to baseline after the deescalation of polymyxin B, the patient was in observation in hospital for 17 days and discharged in a hemodynamically stable condition. The adverse drug reporting was done based on Naranjo causality assessment scale and classified as probable ADR [10].

Discussion

Polymyxins are reintroduced for the treatment of MDR gram negative organisms, although sufficient data is available regarding the nephrotoxicity and neurotoxicity of poly B very few data is available regarding the cardiovascular effects of poly B.

The proposed hypothesis regarding for the cardiovascular effects of polymyxin B is assumed due to neuromuscular block i.e., 1) At presynaptic level it decreases the release of acetylcholine and at postsynaptic levels it blocks the release of acetylcholine from the receptor channels leading to significant effect on the action potential of nervous and muscle tissue and it can also non competitively antagonise the acetylcholine active channels on the endplates of post synaptic junction and alter the levels of acetylcholine. 2) The other possible mechanism for cardiovascular effects of polymyxin B is assumed due to prolonged depolarisation phase secondary to calcium depletion caused by polymyxin B, or histamine release causing systemic vasodilation and hypotension [11,12].

Conclusion

With the rise of multidrug resistant organisms the usage of polymyxins will increase in the upcoming future. It is Imperative that all health care professionals who either prescribes or care for patients receiving polymyxin B be aware of their toxic effects and remains vigilant. As MDR bacteria continue to increase the use of polymyxins to combat these infections is likely to become even more widespread.

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