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Case Report

Recurrent Acute Kidney Injury Associated with Inhaled Gentamicin

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Abstract

Purpose: Recurrent nephrotoxicity due to systemic absorption of nebulised gentamicin is reported.

Summary: A 66 years old woman known to have post-tuberculosis bronchiectasis with chronic hypercapnic respiratory failure and diabetes mellitus complicated by diabetic nephropathy Stage 2 with a baseline serum creatinine (Cr) level of 50 - 70 µmol/L.

She had multiple hospital admissions due to infective exacerbations with Pseudomonas species grown from sputum cultures on several occasions with numerous courses of antimicrobial regimens for eradication.

While the patient was receiving nebulised gentamicin (80 mg every 12 hours), it was noted that her Cr started to increase within five days; progressing to acute kidney injury (AKI) (Cr level deteriorated from 95 to 175 µmol/L over ten days). Common causes for AKI were ruled out. A trough gentamicin level was done 30 minutes before the next dose, and it was found to be 0.3 mcg/mL; therefore, gentamicin was stopped with subsequent improvement in the creatinine.

Rechallenge with nebulised gentamicin was carried out by giving a single dose of 80 mg. A random gentamicin level, measured 7 hours after the dose, was 1 mcg/ml which was highly indicative of systemic absorption of the drug.

Another course of nebulised gentamicin (80 mg every 12 hours) was associated with a rise in Cr from 88µmol/L to 116 µmol/L. After excluding the possible causes and given the previous incidents, it was agreed that the creatinine elevation was most likely a side effect of the inhaled gentamicin albeit without a drug level.

Conclusion: Recurrent acute kidney injury associated with inhaled gentamicin suggests possible systemic absorption of nebulised gentamicin may occur in patients receiving this regimen for bronchiectasis.

Keywords: *AKI; Gentamicin; Inhalation; Bronchiectasis*

Abbreviations

AKI: Acute Kidney Injury; BTS: British Thoracic Society; CRRT: Continuous Renal Replacement Therapy; Cr: Creatinine; CF: Cystic Fibrosis; DM: Diabetes Mellitus; DPI: Dry-Powder Inhaler; LTOT: Long-Term Oxygen Therapy; MV: Mechanical Ventilation; MIC: Minimum Inhibitory Concentration; MDRS: Multi-Drug Resistant Organisms; non-CF: Non-Cystic Fibrosis; NIPPV: Noninvasive Positive Pressure Ventilation; PEF: Peak Expiratory Flow; SVN: Small-Volume Nebuliser; VAP: Ventilator-Associated Pneumonia

Introduction

Bronchiectasis is a chronic condition that results in irreversible dilatation of the bronchi. Initially described by Laennec in 1819, patients with bronchiectasis typically suffer from a persistent cough, chronic daily sputum production, recurrent chest infections, and reduced health-related quality of life [1,2].

The estimated prevalence of bronchiectasis (non-cystic fibrosis)-based on narrow case-finding criteria-is 139 cases per 100,000 persons, and it is higher among women and elderly. In bronchiectasis, the airways become chronically infected with a variety of bacterial pathogens. Previous studies have shown that the bacterial load in the airways correlates with the degree of neutrophilic airways inflammation [3,4]. A vicious cycle of infection and inflammation results in frequent infective exacerbations requiring several courses of antibiotics [5,6].

The aerosolised delivery of antibiotics offers an alternative route that facilitates direct antibiotic delivery to the lung. Compared to systemic routes of administration (both enteral and parenteral), inhalation achieves higher pulmonary concentrations of antibiotics, with the potential to reduce systemic toxicity such as nephrotoxicity [7-9]. This is particularly true for aminoglycoside therapy where the common nephrotoxic side effects limit the use of this antibiotic class [10].

Herein, we report a case of recurrent acute kidney injury following administration of nebulised gentamicin for bronchiectasis exacerbation.

Case Report

A 66 years old woman who was known to have post-tuberculosis bronchiectasis with destroyed left lung, chronic hypercapnic respiratory failure (type II) and cor-pulmonale for which she was on noninvasive positive pressure ventilation (NIPPV) and long-term oxygen therapy (LTOT) at home. Her other co-morbid conditions included hypertension, chronic hepatitis C and diabetes mellitus (DM) complicated by severe diabetic neuropathy and diabetic nephropathy Stage 2 (incipient nephropathy) with a baseline serum creatinine (Cr) level of 50 - 70 µmol/L (eGFR 72 - 100 ml/min as calculated using Cockcroft-Gault Equation).

She had multiple hospital admissions due to pneumonia and infective exacerbations of her bronchiectasis. Her sputum cultures showed colonisation with *Pseudomonas* species on several occasions resulting in prescribing numerous courses of antimicrobial regimens for *Pseudomonas* eradication which included oral ciprofloxacin given as outpatient medications, and intravenous Piperacillin/tazobactam or ceftazidime during hospital admission two years earlier.

During her latest admission, her diagnosis was viral pneumonia (H1N1 positive swabs)which was managed with oseltamivir, Piperacillin/tazobactam and linezolid. However, she developed severe hospital-acquired pneumonia with worsening respiratory failure resulting in transfer to the intensive care unit. Her condition was complicated by septic shock requiring vasopressor support along with mechanical ventilation (MV) due to progressive hypercapnia. Moreover, she suffered from acute kidney injury (AKI) that was managed by continuous renal replacement therapy (CRRT) for 48 hours before her renal functions returned to baseline. Due to the difficulty of weaning from MV and failure of extubation trials, she was tracheostomized and remained ventilator-dependant.

She suffered from a protracted hospital stay that lasted over 14 months which was complicated with recurrent episodes ventilator-associated pneumonia (VAP). Her tracheal aspirates revealed multiple growths of multi-drug resistant organisms (MDROs) including *Pseudomonas aeruginosa* and *Acinetobacter baumannii* which were treated with a combination of carbapenem and intravenous colistin. Also, various courses of gentamicin and colistin nebulisation were given either during the infectious exacerbation or in between them as a trial for the eradication of the MDROs as they were sensitive to aminoglycosides and colistin in almost every culture.

Nine months into her hospital stay, the patient was receiving a planned two-week-course of nebulised gentamicin (80 mg every 12 hours) in the medical ward. However, it was noted that her serum Cr started to increase within five days from initiation (Figure 1). This soon progressed to frank AKI (Cr level deteriorated from 95 to 175 µmol/L over ten days). Common causes for AKI such as dehydration, hypoperfusion, severe sepsis and nephrotoxic medications along with possible post-renal causes were ruled out leading to the suspicion that nebulised gentamicin might be the culprit behind that event although nephrotoxicity is not a known side effect of inhaled gentamicin.

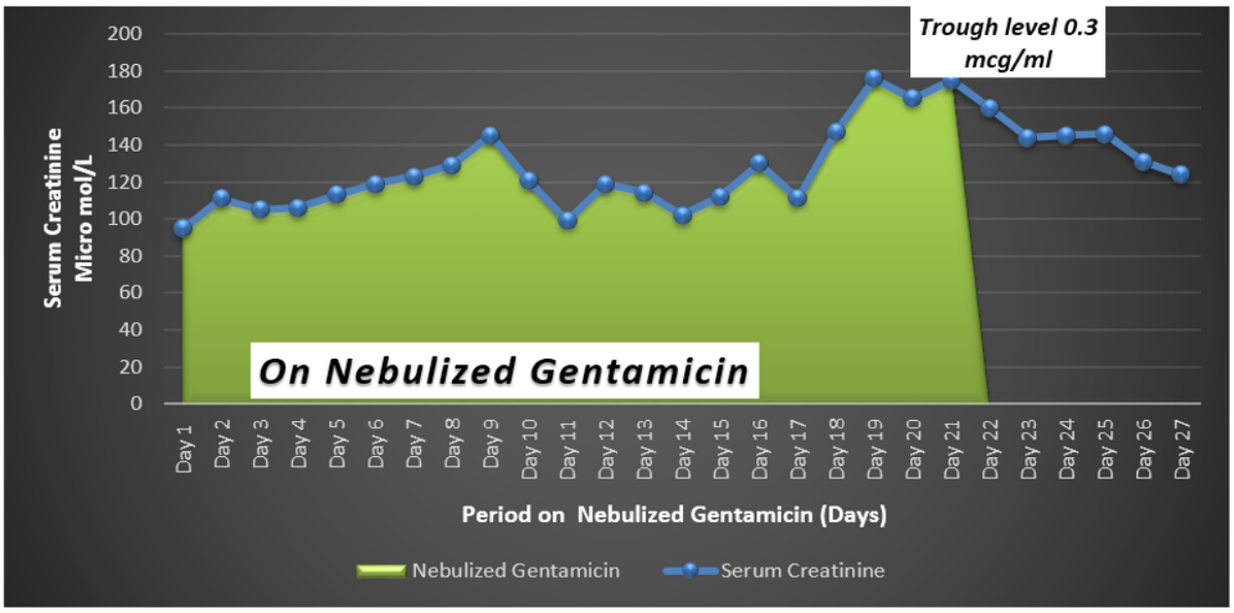

Figure 1: *The changes in serum creatinine while receiving nebulized gentamicin.*

Therefore, trough gentamicin level was done 30 minutes before the next dose, and it was found to be 0.3 mcg/mL; subsequently, gentamicin was stopped. Afterwards, at day 21, her serum Cr level was back to the baseline. To test this hypothesis, rechallenge with nebulised gentamicin was carried out by giving a single dose of 80 mg nebulised gentamicin. A random gentamicin level, measured 7 hours after the dose, was 1mcg/ ml which was highly indicative of systemic absorption of the drug.

Around three months later, another course of nebulised gentamicin (80 mg every 12 hours) was prescribed to the patient by another treating team with a subsequent rise in her Cr level from 88 µmol/L up to 116 µmol/L, but trough level was not measured. After excluding possible causes for the elevation in her creatinine and given the previous incidents, all the treating teams agreed the elevation of creatinine was most likely a side effect of the inhaled gentamicin and decided to avoid it later for this patient.

Retrospectively, we investigated all the previous courses of nebulised gentamicin and tried to find out if there was a concomitant rise in the serum Cr during its administration. We found out that four out of five previously administered courses of inhaled gentamicin were associated with an increase in the serum creatinine by 30% to 80% of her baseline at the time of drug initiation (Figure 2).

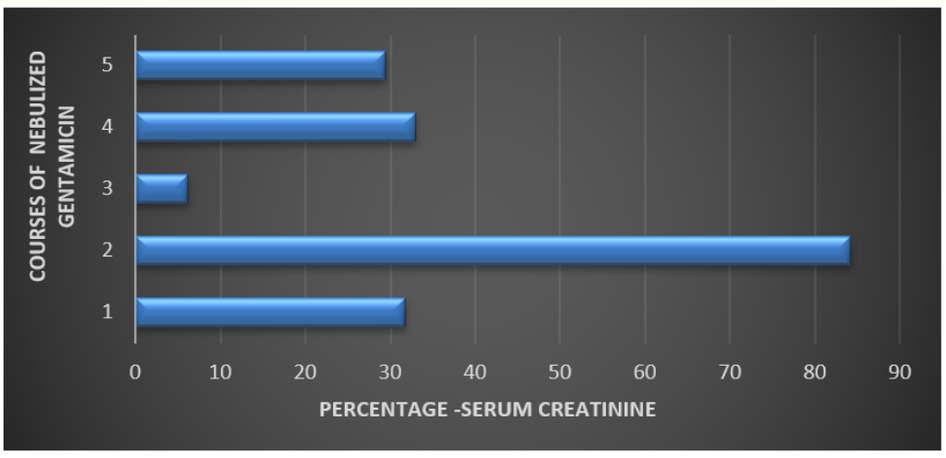

Figure 2: *The courses of nebulized gentamicin received over last 5 years and the percentage increase in serum creatinine.*

Discussion

We describe a patient with non-cystic fibrosis bronchiectasis whose airways were chronically colonised with *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. This resulted in many infective exacerbations. She received multiple courses of nebulised gentamicin aiming at reducing the bacterial load while simultaneously avoiding the toxicity of systemic antibiotics.

This practice is in line with British Thoracic Society (BTS) guidelines that encourage the use of long-term nebulised antibiotics for patients who have more than three exacerbations per year requiring antibiotic therapy or patients with fewer exacerbations that cause significant morbidity [11]. In such patients, long-term nebulised antibiotics should be considered if chronically colonised with *Pseudomonas aeruginosa* [11].

Aminoglycosides and colistin are the most common antibiotics compounded from IV formulation for nebulisation in bronchiectasis. Use of inhalational antibiotics is "off-label" for the non-cystic fibrosis (non-CF) bronchiectasis patients because most of supporting data come from the cystic fibrosis (CF) patients. Several studies performed in the non-CF bronchiectasis have shown that inhaled antibiotics, such as inhaled tobramycin, reduce the bacterial load of *Pseudomonas* in the airways resulting in fewer exacerbations or hospitalisations [12].

In a randomised double-blinded study with 28 pts with bronchiectasis, a short course of aerosol therapy (3d) with gentamicin 40 mg resulted in decreased sputum myeloperoxidase, reduced sputum volume, reduced bacterial load and improved peak expiratory flow (PEF) rates and 6 minutes walk test compared to 0.45% saline twice per day [12].

The patient in this case report developed AKI following a course of nebulised gentamicin. At that time, she was not hypoperfused, receiving any nephrotoxic medication, dehydrated or in severe sepsis. Trough gentamicin level was 0.3 mcg/mL, which was suggestive of systemic absorption of nebulised gentamicin. The random gentamicin level (1 mcg/mL) measured after rechallenging her with nebulised gentamicin was very high despite being after a single dose as it was equivalent to target trough levels of intravenously administered gentamicin after reaching steady state. Another incidence of a rise in serum Cr following nebulised gentamicin three months later was observed. In both occasions, the patient was not on any other nephrotoxic medications.

Naranjo Adverse Drug Reaction Probability Scale for our patient is eight which indicates a "probable adverse drug reaction". The Naranjo score may have its limitations in evaluating adverse drug reaction in critically ill patients such as difficulty to re-challenge patients, inapplicability of placebo administration, possible lack of serum drug concentrations and clarification of objective measurement.

In this patient, the rise in serum Cr was documented to recur after re-administration of nebulised gentamicin; however, we do not have a dose-response relationship of the medication and the adverse reaction [1].

Our findings of increased gentamicin level in blood following nebulised gentamicin was supported by the study of Maeve., *et al.* that included 65 patients with non-CF bronchiectasis. They were randomised to receive either nebulised gentamicin (80 mg twice daily) or 0.9% saline for 12 months. Serum gentamicin levels, urea, and electrolytes were measured two weeks after treatment initiation followed by monthly evaluation of the three parameters until the completion of the study and three months after completion of therapy. Serum gentamicin levels at the end of treatment were 0.13 (0 - 0.37) mg/ml. Only one patient developed a serum gentamicin level higher than 1 mg/ml during the study which occurred during month 9 of therapy (level 1.25 mg/ml) and after reduction of study treatment to a once-daily-dose all subsequent levels (at weekly intervals for three weeks) were less than 1 mg/ml for the subject concerned [1].

Our patient developed two episodes of AKI following a short course of nebulised gentamicin, five days in the first episode and ten days following the second.

In an old pilot study, ten patients with CF or non-CF bronchiectasis, who were chronically infected with *Pseudomonas aeruginosa*, were randomised to receive single-dose and triple crossover protocol of either gentamicin 160 mg via dry-powder inhaler (DPI) or small-volume nebuliser (SVN), or gentamicin at 5 mg/kg by intravenous infusion. In seven of the 10 patients, the minimum inhibitory concentration (MIC) was achieved in sputum after DPI and SVN, with mean gentamicin concentrations at 2h after administration of 13.1 mg/g sputum (range: 2.2 to 23.9 mg/g) and 97.2 mg/g sputum (range: 0.3 to 194.2 mg/g), respectively. However, blood concentrations following inhaled gentamicin were minimal and were below concentrations known to cause systemic toxicity as nephrotoxicity (urine gentamicin levels were approximately 40 to 600-fold greater after intravenous than after SVN or DPI dosing administration respectively (p-value < 0.01) [2]. Very few studies were conducted following this study to investigate the potential nephrotoxicity of nebulised gentamicin in patients with bronchiectasis.

This case report suggests that systemic absorption of nebulised gentamicin can result in acute kidney injury in patients with bronchiectasis; therefore, monitoring of kidney function might be warranted during nebulization therapy. Further randomised controlled studies needed to confirm these findings in patients with CF or non-CF bronchiectasis.

Conclusion

Recurrent acute kidney injury associated with inhaled gentamicin suggests significant systemic absorption of nebulised gentamicin in patients with bronchiectasis.

Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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