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Acute Renal Failure Due to Inhaled Tobramycin. A Case Report

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1. Abstract

Inhaled tobramycin is a treatment option to treat respiratory infections caused by Pseudomonas aeruginosa, allowing high concentrations of this antibiotic in the respiratory tract, reducing secondary toxicity. However, nephrotoxicity is possible due to drug absorption, especially in patients with previous kidney disease. We explain the case of a 68-year-old man with a kidney transplant who presents acute kidney failure after receiving inhaled tobramycin. After starting the treatment, he presented two admissions for acute renal failure. The first one coinciding with the start of treatment and the second one on the third day after restarting it, after the rest cycle. It would be advisable to monitor tobramycin serum levels even when the drug is administered nebulized / inhaled, especially in those patients risk factors for nephrotoxicity. In patients with chronic kidney disease, we recommend not administering inhaled tobramycin if there are other treatment options.

2. Introduction

Aminoglycosides are often used to treat respiratory infections caused by Pseudomonas aeruginosa [1-3]. However, adequate pulmonary drug concentrations with intravenous treatment can cause nephrotoxicity and ototoxicity. Inhaled tobramycin is a treatment option, allowing high concentrations of this antibiotic in the respiratory tract, reducing secondary toxicity due to the reduction of systemic absorption [4]. Absorption through the respiratory tract epithelium is minimal and no randomized clinical trials reporting toxicity [5-6]. As a result, serum aminoglycoside concentrations are not routinely monitored in those patients. Although there are cases described of nephrotoxicity and ototoxicity due to inhaled tobramycin, the evidence is still scarce. In this article, we explain the case of a 68-year-old man with a kidney transplant who presents acute kidney failure after receiving inhaled tobramycin.

3. Case Report

68-years-old men, with previous hypertension, diabetes mellitus on insulin treatment, former smoker, Addison's disease on hormone replacement therapy and chronic renal insufficiency. He had received a renal transplant on 2005. Later, he has developed chronic graft dysfunction with basal creatinine around 1.3 - 1.5 mg/dl and a lymphoproliferative disease in the post-transplant period (lymphoproliferative intestinal lymphoma type B diffuse large cell lymphoma), treated with rituximab, currently in remission. Actually, he receives immunosuppressive treatment with Sirolimus, Mycophenolic acid and Prednisone.

His medical record includes extrinsic bronchial asthma with home oxygen therapy, bibasal bronchiectasis with recurrent respiratory infections and permanent colonization of the airways by multi-resistant Pseudomonas aeruginosa. He was in chronic treatment with inhaled colistin since 2015. In May 2020, it was changed to nebulized tobramycin 300 mg every 12 hours, in 28-day on / off cycles.

In July 2020, he was admitted for oligoanuric acute renal failure (AKIN III) which is attributed to hypovolemia consequence of gastrointestinal diseases (maximum creatinine: 5.53 mg/dl) and severe metabolic acidosis. He receives treatment with intravenous

fluids and bicarbonate. He initially requires vasoactive support with intravenous norepinephrine infusion. He received empirical antibiotic for abdominal infections and persistent colonization by Pseudomonas aeruginosa with Metronidazole and Piperacillin-Tazobactam for 10 days, without microbiological isolation in blood cultures or stool test. The clinical evolution was favorable. He recovered renal function up to baseline creatinine levels of 1.8 mg / dl, being discharged after 10 days of admission. During admission, the nebulizations with tobramycin were temporarily suspended.

One month later, in August 2020, he was admitted with a diagnosis of oligoanuric acute renal failure and metabolic acidosis secondary, with no signs of hypovolemia or apparent trigger. The first day of admission, he presented creatinine of 3.07 mg / dl, in urine: sodium 80 mmol / L, EFNa> 1%, protein / creatinine ratio 1.5; with maximum creatinine during admission of 8.03 mg/dl. Although he did not present clinical data suggestive of infection, due to elevation of acute phase reactants and the patient's medical history, the respiratory focus is empirically covered with intravenous piperacillin-tazobactam for 14 days.

Reviewing the patient's medical history, the only significant antecedent is a change of medication in May 2020 to inhaled Tobramycin. After starting the treatment, he presented two admissions for acute renal failure. The first one coinciding with the start of treatment, and the second one on the third day after restarting it, after the rest cycle.

Because inhaled tobramycin could be the cause of renal function deterioration, this drug was discontinued during the second admission. Serum tobramycin levels were requested. Two measurements were made when we suspect the diagnosis. Tobramycin measurements were performed on the serum obtained the previous days. The first one 20 hours after the last nebulization of the drug, with levels of 0.90 ug / mL. The second one 48 hours after the last nebulization, with levels of 0.40 ug / mL.

After tobramycin treatment was stopped, a progressive improvement in renal function is observed up to baseline creatinine levels. After 13 days of hospitalization, the patient had a high creatinine level of 1.90 mg / dl and it was normalized later. The patient has not had any further episodes of acute renal failure after definitively stopping inhaled tobramycin.

4. Discussion

Bronchiectasis is a chronic inflammatory disease of the airways that consists of abnormal dilation of the bronchi, with chronic inflammation and destruction of the bronchial wall. Structural alterations facilitate colonization by potentially pathogenic microorganisms, which cause frequent lung infections associated with greater morbidity, poor quality of life, and increased mortality [7]. European guidelines recommend the use of long-term inhaled antibiotics in patients with bronchiectasis and colonization of the airway by P. aeruginosa, who present three or more exacerbations per year [8]. This is the case of our patient.

Tobramycin has shown intense activity against Pseudomona aeruginosa. Inhaled administration allows obtaining a high concentration in the airway with minimal systemic effects. Therefore, this is a great alternative for this kind of patient. Systemic absorption of inhaled tobramycin (TOBI) is generally minimal. Several randomized controlled trials [4, 5] confirm the safety of this mode of administration. However, these studies are old. Actually, there is described some case of acute renal failure probably related to inhaled tobramycin.

Izquierdo et al [9] describe the case of a 73-year-old woman, with previous normal renal function, who presented oliguric acute renal failure after 4 days since the start of TOBI (300 mg every 12 hours), with a maximum creatinine of 875.2 mol / l (9.9 mg / dl). The serum levels of tobramycin after 8 hours since the last administration were 5.4 µg / ml (considered toxic).

The patient required 3 hemodialysis sessions for full recovery of kidney function (after 25 days). In our case study, elevated levels of tobramycin were also detected in blood (levels of 0.9 µg / ml after 20 hours since the last administration). Although these levels are not into toxic range, the patient probably had higher levels within a few hours of administration, which could be sufficient to produce important systemic side effects similar to those produced by intravenous administration. The Clinical Analysis Service informed us that the relationship between both values indicates that the elimination half-life of tobramycin in this patient would be around 48 hours.

Therefore, even if the concentration is not nephrotoxic, it does appear that there is a causal relationship between the initiation of inhaled tobramycin and the worsening of renal function.

Cases of elevated levels of tobramycin in blood, had been described after inhaled administration in patients with decreased renal function [10,11]. In the case study published by Langley A et al [10], they present a 79-year-old man with medical record of chronic kidney disease. This patient presents severe respiratory failure requiring mechanical ventilation, and in this context, worsening kidney function requiring hemodialysis. In the sputum culture, P. aeruginosa was isolated, so the patient started inhaled tobramycin. It was decided to measure the levels of tobramycin in blood. They observed a concentration of 0.2 mg / mL after two hours since the first administration. On the third day the concentration was 1.6 mg / mL approximately after 1.3 hours since drug administration. The concentration decreased to 0.8 mg / mL on the morning of the 4th day (with the absence of drug administration the previous night). On the 5th day it was 2.1 mg / mL after 2 hours since administration. Two days after stopping the drug, the levels were undetectable.

Inhaled tobramycin is also frequently used in patients with cystic fibrosis.

Hoffman et al [12] report the case of a 20-year-old woman with cystic fibrosis and respiratory infection due to Pseudomonas aeruginosa. This patient initially received ciprofloxacin. 3 weeks later, as the patient still has the symptoms, inhaled tobramycin was added to treatment. One week later, he was admitted due to worsening of the respiratory symptoms and laboratory abnormalities. Non-oliguric acute renal failure with creatinine 9 mg / dl was observed, without proteinuria and anodyne sediment. The previous renal function was normal. The serum tobramycin levels at hospital admission were 2.8 mg / L. In the electron microscopy of renal biopsy, he presents acute tubular necrosis and cytosegresomes, compatible with aminoglycoside toxicity. Treatment with ciprofloxacin was maintained and tobramycin was discontinued, improving renal function to baseline levels of 0.9 mg / dl.

Most of the data of these case studies correspond to patients with cystic fibrosis, and do not include patients with decreased renal function at the start of treatment [5]. Patients with cystic fibrosis may have altered pharmacokinetics, with a higher volume of distribution and a lower systemic bioavailability of inhaled tobramycin. Therefore, there is a higher clearance of the drug, leading to a lower incidence of nephrotoxicity [13, 14]. In contrast, our patient did not have record of cystic fibrosis, but he had chronic kidney disease with basal creatinine 2 mg / dl. Both factors are able to favor decrease in drug clearance.

Canella et al [15] describe a 62-year-old woman with chronic kidney disease with baseline creatinine 2 mg / dl. The patient was hospital admitted due to a respiratory sepsis with bilateral pneumonia consequence of multidrug-resistant P. aeruginosa, treated with IV tobramycin, piperacillin / tazobactam IV and Imipenem IV. One month after since the end of treatment, she presented a recurrence of infection, receiving IV Imipenem and vancomycin, along with inhaled tobramycin. The patient received inhaled tobramycin for 1 month. During this period creatinine progressively increased to 4.5 mg / dl. The sediment was nondescript and renal ultrasound was normal. Although Imipenem and vancomycin was stopped after 3 weeks, with serum vancomycin levels between 10 and 15 μg / mL, and maximum serum tobramycin levels of 0.7 μg / ml. During the treatment, renal function did not improve. Finally, tobramycin treatment was discontinued, but the patient did not recover renal function and needed to start renal replacement therapy with hemodialysis. The patient had a history of chronic kidney disease that could have contributed to the decreased clearance of tobramycin (as in our patient). However, in this case, a temporal relationship could not be established related to the administration of inhaled tobramycin and the deterioration of renal function.

The safety of inhaled tobramycin in transplant recipients has also not been established. We found two cases [14, 16], corresponding to a lung and heart transplant recipient, respectively. They presented acute renal failure secondary to inhaled tobramycin, suggesting that this drug should be used with caution in this population. A recent study compared the pharmacokinetic profile of tobramycin administered intravenously to patients with cystic fibrosis before and after lung transplantation. Interestingly, after transplantation, a 40% reduction in drug clearance and a 141% increase in elimination half-life were observed. The researchers suggest that the etiology of the change is probably multifactorial. Different factors influence such as age, renal function, nutritional status, and concomitant administration of nephrotoxic agents [14].

In conclusion, it would be advisable to monitor tobramycin serum levels even when the drug is administered nebulized / inhaled, especially in those patients with risk factors for nephrotoxicity. In patients with chronic kidney disease, we recommend not administering inhaled tobramycin if there are other treatment options. This drug should be the last option, with close monitoring of tobramycin levels and kidney function.

5. Statements

5.1. Statement of Ethics

The paper is exempt from ethical committee approval as the authors presented a retrospective observational case.

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