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Case Report

Piperacillin-tazobactam induced hypokalaemia

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ABSTRACT

Electrolytes imbalance has been reported with the use of several antimicrobials in clinical scenarios**.** Piperacillin/tazobactam is a commonly used antibiotic with tolerable side effects and broad antimicrobial activity in general practice. Herein we report a case of a 27 year old male presented with Road Traffic Accident with depressed frontal bone fracture, fracture humerus and fracture of great toe complicated with Ventilator associated Pneumonia (VAP) who developed hypokalemia secondary to intravenous piperacillin-tazobactam. Upon withdrawal of the drug, serum potassium normalized in 2 days. There were no other underlying renal or hepatic illness and other causes of hypokalemia. Hypokalemia is a serious adverse effect of piperacillin-tazobactam and should be suspected while treating patients with this drug in clinical practice especially in Intensive Care Units (ICU). We concluded this causality as probable/likely category according to WHO-UMC Causality Categories.

Keywords: Hypokalemia, Piperacillin/tazobactam, Ventilator associated pneumonia

INTRODUCTION

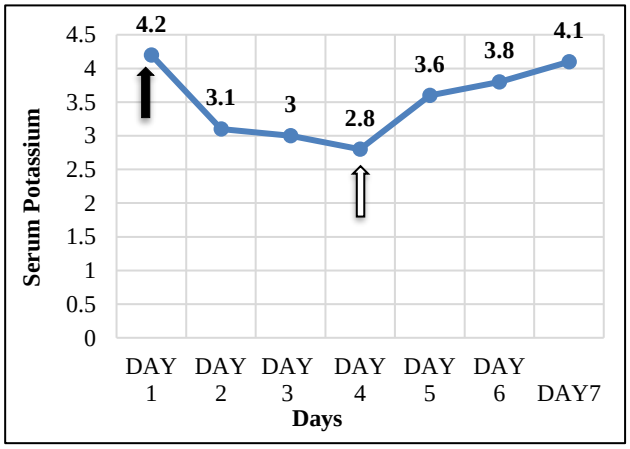
Electrolyte disturbance is a very common entity reported in a medical setting as reported by Karan et al.[1] Piperacillin-tazobactam is a combination of semisynthetic ureidopenicillin (piperacillin) and the β-lactamase inhibitor (tazobactam) and is a commonly used antibiotic with broad spectrum antimicrobial activity and tolerable side effects such as dizziness, nausea, vomiting, abdominal discomfort, headache but in rare instances can also cause muscle cramps and spasm due to hypokalemia, seizures, cloudy urine, new signs of infection or severe skin reactions.[2] Both piperacillin and tazobactam are approximately 30% bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged drug with 68% of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80% of the administered dose excreted as unchanged drug and the remainder as the single metabolite. Till now the potential for pharmacokinetic drug interactions between Piperacillin-tazobactam and aminoglycosides, probenecid, vancomycin, heparin, vecuronium, and methotrexate has been evaluated. Potassium is an important intracellular cation responsible for action potential generation and normal functioning of muscles. Hypokalemia, which is a common electrolyte abnormality,

affects about 20% of people admitted to hospital and is categorized as mild, moderate and severe hypokalemia when serum potassium level is 3.0-3.5mmol/L, 2.5-3.0mmol/L and less than 2.5mmol/L, respectively. Mild hypokalemia is often asymptomatic. Severe hypokalemia is associated with generalized weakness, rhabdomyolysis and paralysis and cardiac arrhythmias.[2]

CASE REPORT

A 27 year old male was brought to Emergency Medicine Department of our hospital with Road Traffic Accident. On investigation, depressed fracture of frontal bone associated with Intracranial Haemorrhage, right proximal humerus fracture and fracture of proximal phalanx of great toe was diagnosed. His investigations on the day of admission were as follows: Hb: 9.0mg/dl, WBC: 14,540cells/cumm, Glucose: 70mg/dL, Creatinine: 0.59mg/dL, Uric acid: 2.9mg/dL, Na: 143mEq/L, K: 4.2mEq/L, Ca: 8.5mg/dL, Mg: 1.9mEq/L, ALT: 58U/L, Total Protein: 5.47gr/dL, Albumin: 2.79gr/dL.

Patient required intubation and mechanical ventilation due to head injury and was tracheostomized subsequently. Initially he was treated with intravenous ceftriaxone along with other supportive therapy, but his WBC counts were increasing due to multiple open wounds and fractures. He also developed Ventilator associated pneumonia (VAP). So, he was given carbapenems for broad spectrum coverage till report of tracheal culture was obtained. After 5 days, Providensia stuartii and Acinetobacter which both were sensitive to piperacillin/tazobactam were isolated from Endotracheal tube drainage culture.



Black arrow shows the beginning and white arrow shows the end of piperacillin/tazobactam administration after which serum potassium levels were back to normal

Figure 1: Serum potassium level during the piperacillin/tazobactam therapy.

Patient was clinically improving so antibiotic was de-escalated again from Meropenem to Piperacillin/Tazobactam. He was started on Inj. Piperacillin/Tazobactam 4.5gm 8 hourly. On Day 2, his serum potassium levels started decreasing to count 3.1mEq/L and dropped to 2.8mEq/L on Day 4 (Figure 1). Despite potassium correction with intravenous KCl 10mEq/hour, his hypokalemia persisted.

Apart from treating with piperacillin-tazobactam, there was no obvious cause (diuretics, alcohol, vomiting, diarrhoea, beta-2 agonist, insulin) for hypokalemia. Hence, drug-induced hypokalemia was suspected in this patient. It was attributed to piperacillin-tazobactam treatment. So, Piperacillin-tazobactam was stopped on the fourth day and was replaced by the consulting physician with Inj. Polymyxin B 5lac units iv TDS and within next 2 days, serum potassium returned to normal. This case was reported via Vigiflow at WHO-UMC with Id-2018-46206.

DISCUSSION

Hypokalemia is serum potassium level less than 3.5mEq/L and is a common electrolyte abnormality in clinical practice. Potassium homeostasis is determined by kidney, and excess potassium is excreted in the urine. The normal range for serum potassium level is 3.5-5mEq/L. Hypokalemia may result from conditions as varied as trans-cellular shift (movement of potassium from serum into cells as a result of insulin use or alkalosis), malnutrition or decreased dietary intake and parenteral nutrition, renal losses such as renal tubular acidosis, Bartter syndrome, Fanconi syndrome, hyperaldosteronism, magnesium depletion, leukaemia, Cushing syndrome, gastrointestinal losses such as vomiting, pyloric stenosis, diarrhoea, enemas or laxative use, gastric aspiration, ileal loop and medication effects. Many drugs may lead to hypokalemia for example diuretics (most common cause), beta-adrenergic agonists, theophylline, steroids, and aminoglycosides.[3] These drugs can lead to hypokalemia in the therapeutic and toxic doses. In this case there were no trans-cellular shift, no renal or gastrointestinal losses.

Table 1: Antimicrobials associated with hypokalemia.

Medication class	Examples of common drugs	Mechanism
Antimicrobials	Nafcillin	Renal potassium loss
	Ampicillin	
	Penicillin	
	Carbenicillin	
	Aminoglycosides*	
	Amphotericin B*	
	Foscarnet*	

*Also associated with magnesium depletion

Piperacillin sodium exerts bactericidal activity by inhibiting septum formation and cell wall synthesis. In vitro, piperacillin is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. Tazobactam sodium is a β-lactamase inhibitor. Tazobactam, in combination with piperacillin enhances and extends the antibiotic spectrum of piperacillin to

include β-lactamase producing bacteria normally resistant to piperacillin. Its' known adverse effects are, mild to moderate in severity and transient nature, hypersensitivity reactions such as rash and pruritus; gastrointestinal system disorders such as diarrhoea, nausea and vomiting; haematological disorders such as thrombocytopenia and neutropenia and rarely haemolytic anemia, hepatotoxicity, electrolyte and acid-base disturbances.[3] Polderman et al, reported that treatment with piperacillin may cause or aggravate electrolyte disorders and tubular dysfunction in intensive care unit patients even when serum creatinine levels remain normal. Zaki et al, reported a case of a 2-year-old girl who developed hypokalemic metabolic alkalosis and bradycardia after receiving intravenous piperacillin/tazobactam for bronchopneumonia.[4,5] Similarly, Hussein et al, reported severe hypokalemia secondary to piperacillin/tazobactam in a patient with normal renal function.[6] Two hypotheses have been put forward for explaining the mechanism of hypokalemia. Piperacillin-sodium behaves as nonabsorbable anions enhancing transepithelial electronegativity in the distal nephron, resulting in increased distal sodium delivery and potassium excretion**.** According to second hypothesis, the large amounts of sodium administered with piperacillin can result in solute diuresis. A solute diuresis causes a high flow rate in the cortical collecting duct and potassium excretion through the so-called BK (Big Potassium) channels.[7,8]

In individuals with liver diseases or those receiving cytotoxic therapy or diuretics, piperacillin/tazobactam has been reported rarely to produce a decrease in serum potassium levels at high doses of piperacillin.[9] There were no different causes that facilitated hypokalemia such as hepatic or renal failure in this patient. The usual total daily dose of piperacillin sodium/tazobactam sodium for adults is 12g/1.5 g, given as 3g/0.375 g every six hours. In this case, hypokalemia was seen after 2 days of intravenous piperacillin/tazobactam administration at doses of 4g/500 mg every eight hours. Piperacillin/tazobactam was monotherapy in this patient, none of aminoglycoside or other antibiotics were administered.

Evaluation and management of a hypokalaemic patient should include a careful review of medications history to determine if a drug capable of causing or aggravating this electrolyte abnormality is present.[10]

CONCLUSION

In conclusion we must keep in the mind that even if renal and hepatic functions are normal and in the absence of other medications such as diuretic, laxatives etc., piperacillin/tazobactam may be cause of severe hypokalaemia and related life threating complications such as cardiac arrhythmia. Thus, Periodic electrolyte assessment should be performed in patients who are receiving piperacillin/tazobactam.

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REFERENCES

1. Shah KB, Gupta SD, Rana DA, Malhotra SD. Patel PR. Analysis of drug related electrolyte disturbances in emergency medicine department. Int J Basic Clin Pharmacol. 2018;7:2005-9.
2. Ben Salem C, Hmouda H, Bouraoui K. Drug-induced hypokalaemia. Curr Drug Saf. 2009;4(1):55-61.
3. Kutluturk F, Uzun S, Tasliyurt T, Sahin S, Barut S, Ozturk B, et al. A Rare Complication of Antibiotic (Piperacillin/Tazobactam) Therapy: Resistant Hypokalemia. J Med Cases North America; 2012.
4. Polderman KH, Girbes AR. Piperacillin-induced magnesium and potassium loss in intensive care unit patients. Intensive Care Med. 2002;28(4):520-2.
5. Zaki SA, Lad V. Piperacillin-tazobactam-induced hypokalemia and metabolic alkalosis. Ind J Pharmacol. 2011;43(5):609-10.
6. Hussain S, Syed S, Baloch K. Electrolytes imbalance: a rare side effect of piperacillin/ tazobactam therapy. J Coll Physicians Surg Pak. 2010;20(6):419-20.
7. Kokot F, Hyla-Klekot L. Drug-induced abnormalities of potassium metabolism. Pol Arch Med Wewn. 2008;118(7-8):431-4.
8. Kunder SK, Chogtu B, Avinash A, Pathak A, Patil N, Adiga S. A Case Series of Piperacillin-Tazobactam Induced Hypokalemia in a Tertiary Care Hospital in South India. Online J Health Allied Scs. 2015;14(4):17. Available at: http://www.ojhas.org/issue56/2015-4-17.html
9. Tripathi KD. Beta-Lactam antibiotics. Essentials of medical pharmacology. Jaypee publishers. 7th ed; 2013:724.
10. Greenbaum LA. Electrolytes and acid base disorders. In: Behrman RE, Kliegman RM, Jenson HB, Stanton FB, editors. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: WB Saunders; 2008:267-309.

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