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Acute Kidney Injury Due to Vancomycin and Piperacillin-Tazobactam: How Real Is the Risk?

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Introduction

Acute kidney injury (AKI) is defined by an acute reduction in kidney function as identified by an increase in the serum creatinine and reduction in urine output (Harty, 2014). It is a new term coined for the acute renal failure as the injury of the kidney begins long before the significant loss of excretory kidney function that can be detected in laboratory tests (Bellomo, Kellum, & Ronco, 2012). Despite updated clinical definition and staging, development of new renal biomarkers for diagnosis and a better understanding of the pathophysiology, AKI remains the global public health concern (Zuk & Bonventre, 2016). The development of AKI is associated with poor outcomes in hospitalized patients, with increased morbidity and mortality.

AKI occurs in up to 23% of hospitalized patients with an associated mortality of 11%. In the intensive care unit (ICU), AKI rates are increased with the documented incidence of up to 66% and a comparable increase in ICU mortality (Hammond., *et al.* 2017). Drugs are among the most common causes of AKI in both hospital and community settings. Present knowledge suggests that pathophysiologic mechanism of drug-induced nephrotoxicity is complex and often mediated through alteration of interglomerular hemodynamics, impaired tubular secretion, inflammation, uric acid deposition, rhabdomyolysis, and thrombotic microangiopathy (Ghane Shahrbaf & Assadi, 2015).

Risk factors for drug-induced AKI include underlying renal disease, diabetes, hypotension, sepsis, volume depletion, human immunodeficiency virus, and advanced age (Al Yami, 2017). According to Acute Dialysis Quality Initiative (ADQI), the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria was created on the basis of changes in serum creatinine or urine output as a new classification for AKI (The Cleveland Clinic Foundation, 2010). Vancomycin, a glycopeptides antibiotic is a drug of choice for the treatment of severe Gram-positive infections, together with methicillin-resistant Staphylococcus aureus, methicillin-resistant coagulase-negative Staphylococci, and non-vancomycin-resistant Enterococci.

Category	GFR Criteria	Urine Output Criteria
RISK	Increased creatinine ×1.5GFR decrease > 25%	UO < 0.5 mL/kg/h × 6 hr
INJURY	Increased creatinine ×2GFR decrease >50%	UO < 0.5 mL/kg/h × 12 h
FAILURE	Increase creatinine ×3GFR decrease >75%	UO < 0.3 mL/kg/h × 24 hr Anuria × 12 hr
LOSS	Persistent ARF = complete loss of kidney function > 4 weeks	
End-stage kidney disease	End-stage kidney disease (> 3 months)	

ARF, acute renal failure; GFR, glomerular filtration rate; UO, urine output

Table 1: *RIFLE Criteria.*

Vancomycin is primarily excreted through the kidneys with 90% by glomerular filtration and active tubular secretion. The incidence of nephrotoxic events among patients receiving vancomycin has gradually increased, with reported rates of 5-43% depending on the study population. The hypothesized mechanism of vancomycin-associated nephrotoxicity includes drug-induced oxidative stress and mitochondrial dysfunction or cell necrosis in the cells of the proximal renal tubule (Bamgbola, 2016). On the other hand, piperacillin-tazobactam, a β-lactam/β-lactamase inhibitor combination is frequently used alongside with vancomycin as empirical therapy for several infections, including nosocomial pneumonia, abdominal infection, skin and soft-tissue infection, sepsis, and osteomyelitis.

Although nephrotoxicity rates are low when used as monotherapy, higher incidence rates ranging from 16% to 37% have been observed when piperacillin-tazobactam is concomitantly used with vancomycin, suggesting the potential for an additive renal effect between the two agents (Siami, Christou, Eiseman, & Tack, 2001). Vancomycin and piperacillin-tazobactam were the empirical combination therapy for more than a decade, but high rates of AKI has been noted in the recent years (Karino., *et al*. 2016). Several studies indicate that the combination of vancomycin and piperacillin-tazobactam increases the odds of having AKI approximately by three-fold (Luther., *et al*. 2017). Therefore, regular monitoring and precautions are needed to use these drugs.

Patients with AKI have more prolonged hospital length of stay, increased hospital costs, and higher mortality (Murugan & Kellum, 2011). The best way to manage drug-induced AKI includes common preventive strategies including assessment of baseline creatinine clearance or glomerular filtration rate and adjusting medication dosing per the renal function. Identification of nephrotoxic medications and potential nephrotoxic combinations is vital. Additionally, drugs should be prescribed for the shortest period using the lowest effective dose with monitoring of drug concentrations (if possible). Renal function should also be monitored frequently with subsequent medication changes or cessation (Pazhayattil & Shirali, 2014).

We need to understand which populations are at highest risk for drug-associated AKI and encourage judicious use of nephrotoxic medications with frequent monitoring, particularly when a combination of nephrotoxic agents is used. Suspension of offending medications and supportive therapy are the cornerstone of treatment for drug-induced AKI. Once kidney injury is established, the only useful measures are to avoid additional insults, nephrotoxic agents, and further deterioration (Makris & Spanou, 2016). The preventative measures described earlier are therefore essential in therapeutic strategies as well (Khan, Loi, & Rosner, 2017).

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