Clinical Pharmacology & Toxicology Pearl of the Week

~ Vancomycin Associated Acute Kidney Injury ~

Case

- ✓ A 56 y/o female presents with fever, hypotension, and a new heart murmur on physical exam. She has a history significant for type 2 diabetes (A1C 9.3%), stage 3A CKD (creatinine 110 umol/L), obesity (120kg), hypertension, and IV opioid abuse.
- ✓ The admitting team suspects endocarditis. Treatment includes volume resuscitation, management of her diabetes with basal and short acting insulin, and empiric antibiotic therapy with vancomycin 2g Q12H and ceftriaxone 2g Q24H. Upon stabilization, her home antihypertensives ramipril and hydrochlorothiazide are restarted. Ceftriaxone is stopped day 3 when blood cultures reveal MRSA.
- ✓ On day 7 of therapy, her creatinine climbs to 180 umol/L. What are her modifiable and non-modifiable risk factors for AKI, and how will you manage this patient?

Background

- ✓ Drug induced acute kidney injury is defined as a 50% increase in creatinine or absolute increase of 44 µmol/L over 24 – 72 hours, with a minimum of 24-72 hours of drug exposure.
- ✓ Risk of vancomycin induced kidney injury is related to co-morbidities (particularly underlying renal dysfunction), co-prescribing of other nephrotoxic agents, the dose and duration of therapy.
- ✓ Treatment includes prevention by minimizing risk factors, cessation of therapy, and transitioning to alternative agents.

Pharmacokinetics of Vancomycin

- ✓ Vancomycin has negligible oral bioavailability and is 100% bioavailable via the IV route.
- ✓ Vancomycin is a large (1450 daltons) molecule that is 50% protein bound. It is not removed from the plasma by traditional low-flux dialysis filters but can be removed with modern high-flux dialysis filters.
- ✓ Vancomycin undergoes no metabolism and is cleared completely by the kidneys.

Historical Vancomycin Factors Attributed to Nephrotoxicity

- ✓ Vancomycin was originally isolated from soil samples in Borneo and found to be produced by *Amycolatopsis orientalis.*
- ✓ Purification of the drug was difficult and termed "Mississippi Mud" due to its discoloration and impurities. In this form, it has a high incidence of oto- and nephrotoxicity.
- ✓ Newer formulations are 90-95% purified vancomycin and have reported rates of nephrotoxicity between 5-40%.

Controversy Surrounding Vancomycin Associated Nephrotoxicity and Mechanisms

- ✓ Identifying vancomycin induced nephrotoxicity is difficult due to co-administration of nephrotoxic medications, acute illness, and general difficulty identifying a temporally related medication as a causative. Nephrotoxicity is frequently attributed to a different disease process or medication.
- ✓ The two leading mechanisms of vancomycin induced nephrotoxicity include:
  - Immune mediated acute interstitial nephritis, often accompanying other immune mediated reactions such as DRESS, erythema multiforme, and toxic epidermal necrolysis (TEN).
  - Acute tubular necrosis due to vancomycin-uromodulin casts or direct tubular toxicity due to mitochondrial inhibition and oxidative damage.

Risk Factors for Vancomycin Associated Nephrotoxicity

- ✓ Risk factors can be divided into patient-specific and medication-specific factors.
- ✓ Increasing trough levels from 10 mg/L to 15 mg/L and to > 20 mg/L increases the risk of nephrotoxicity from 5% → 10-20% → 33%.
- ✓ Continuous infusions have been found to have a risk ratio 0.6-0.8 compared to intermittent infusions, though no mortality benefit is seen.
- ✓ Duration of therapy >7 days shows a significant increase
- ✓ in risk of nephrotoxicity, with a 4-12% increased odds ratio for each additional day of therapy.

Patient Factors	**Medication Factors**
Obesity	Higher trough levels
Underlying kidney disease	Intermittent infusions
Severity of Illness	Duration of therapy
Concurrent nephrotoxic medication exposure	Total daily dose >4 g
Older age	Higher Area Under the Curve

Back to the Case

- ✓ This patient meets the definition of a drug-induced acute kidney injury with an increase in her creatinine of 70 µmol/L occurring after a minimum of 24-48 hours of exposure to the medication.
- ✓ Her non-modifiable risk factors include her underlying renal disease, obesity, and type-2 diabetes.
- ✓ Her modifiable risk factors include exposure to other nephrotoxic medications including ramipril and ceftriaxone, along with her acute illness and hydrochlorothiazide predisposing her to volume depletion and hypotension, leading to decreased renal perfusion.

Management of Vancomycin Associated Nephrotoxicity

- ✓ Prevention is key!
  - Avoid co-administration of nephrotoxic medications.
  - Treat underlying co-morbid and acute conditions, including volume depletion and hypotension.
  - Use weight-based dosing based on recommendations for a given condition, with a maximum of 2 g at once, or 4 g a day.
  - Adjust frequency of doses based on current renal function.
  - Target minimum vancomycin trough levels indicated for a given condition.
  - Monitor trough levels prior to the 4th dose, with ongoing monitoring based on changes to the patient's renal function and dose adjustments. Involve pharmacist team members in your care plan.
  - Use weight-based dosing, with a maximum of 2 g at once, or 4 g a day.
  - Monitor culture results and tailor therapy once sensitivities return.
- ✓ After development of nephrotoxicity
  - Verify temporal relation required to define a drug-induced acute kidney injury.
  - Discontinue all nephrotoxic medications.
  - Involve infectious disease specialists & transition to another antibiotic regimen with appropriate coverage.
  - If no alternative agents available, can consider ongoing vancomycin therapy while discontinuing other nephrotoxic medications and maintaining adequate renal perfusion. Follow trough levels closely.
  - Dialysis can be considered for typical acute renal failure indications.
- ✓ 75% of patients will have improvement or resolution within 7 days.

References:

1. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. Clin Pharmacol Ther. 2017;102(3):459–469.
2. Luque Y Louis K Jouanneau C Placier S Esteve E Bazin D Rondeau E Letavernier E Wolfromm A Gosset C Boueilh A Burbach M Frère P Verpont MC Vandermeersch S Langui D Daudon M Frochot V Mesnard L Vancomycin-Associated Cast Nephropathy. J Am Soc Nephrol. 2017; 28: 1723–1728.
3. Perazella MA. Pharmacology behind Common Drug Nephrotoxicities. Clinical Journal of the American Society Nephrology . 2018; 13(12):1897-1908.
4. Awdishu L & Mehta RL. The 6R's of drug induced nephrotoxicity. BMC Nephrology. 2017;18:124
5. Reynolds, L.A. & Tansey, Tilli. (2008). Superbugs and superdrugs: a history of MRSA.
6. Sundhu M, Mohapatra S, Arobelidze S, et al. Infective Endocarditis in a Patient with Celiac Disease after Central Venous Catheter Insertion. Cureus 9(2): e1027. doi:10.7759/cureus.1027

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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