Renal Transporters - pathophysiology of drug-induced renal disorders

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Renal Failure

- Up to 25% of acute renal failure is drug induced
- Drug-induced renal injury can present as
  - Acute renal failure
  - Chronic renal failure
  - Nephrotic syndrome
  - Or tubulopathy
- Up to 15% of drug-induced acute renal failure is caused by hypersensitivity reactions that cause renal tubular and interstitial inflammation
Acute Renal Failure

- Drugs can cause acute renal failure by causing
  - Pre-renal
  - Intrinsic or
  - Post-renal toxicity
Pre-Renal Failure

- Drugs can reduce the renal blood perfusion by modulating vasomotor tone
  - Afferent (pre-glomerular)
  - Efferent (post-glomerular) arterioles
- Decreasing glomerular filtration rate with subsequent renal failure
Pre-Renal Failure

Pathophysiology of Prerenal AKI

ACE-I and ARBs decrease renal filtration by inhibiting angiotensin II-mediated vasoconstriction at the efferent arteriole.

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin-induced afferent arterial dilatation.
Pre-Renal Failure

- Renal blood flow is impaired
- Patients will present with low urine output, low sodium excretion and high osmolality
- The urea:creatinine ratio is usually more than 20 as the low urine flow facilitates a disproportionate urea reabsorption relative to creatinine
- The urine sediment is clear

Acute renal failure
Pre-renal failure
Impaired glomerular haemofiltration
  - ACE inhibitors
  - Angiotensin receptor blockers
  - NSAIDs
  - COX-2 inhibitors
  - Diuretics
  - Calcineurin inhibitors (cyclosporin, tacrolimus)

Important clinical and laboratory findings:
- Urinary sodium excretion decreased
- Urinary sediment clear
Intrinsic (inside) Renal Failure

• Intrinsic renal failure
  – Tubular necrosis (e.g. Aminoglycoside antibiotics and amphotericin B)
  – Interstitial nephritis
  – Thrombotic angiopathy (e.g. cyclosporin, tacrolimus)
    • Formation of drug-dependent antibodies or causes direct tissue toxicity that results in the formation of platelet-rich thrombi in small arterioles or capillaries

• Are common causes of parenchymal drug-induced renal injury
Acute tubular necrosis (ATN) is a medical condition involving the death of tubular epithelial cells that form the renal tubules of the kidneys. ATN presents with acute kidney injury (AKI) and is one of the most common causes of AKI. Usually caused by direct drug toxicity, but prolonged impaired renal perfusion may also cause tubular damage.
Acute Tubular Necrosis - Renal Failure

- Chronic injury causes dysfunction of the tubular epithelial cells, which triggers release of fibrogenic cytokines and recruitment of inflammatory cells to injured kidneys.
Acute Tubular Necrosis - Renal Failure

- Patients present with a sudden rise in creatinine concentration, and develop oliguria if the offending drug is continued
  - Urine output less than 400 mL or 500 mL per 24h in adults - ~17 - 21 mL/hour
- Urinary sodium excretion is increased
- Urinary sediment contains granular casts and renal epithelial cells
  - Coarse or fine particulate cellular debris and other proteinaceous material,
- The injury is dose dependent and generally resolves with discontinuation of the causative drug
Acute Tubular Necrosis - Renal Failure

Intrinsic renal causes
Acute tubular necrosis
Aminoglycosides
Amphotericin B
Cisplatin
Radiocontrast media

Important clinical and laboratory findings:
Sudden rise in creatinine
Urinary sodium excretion increased
Urinary sediment: granular casts and renal epithelial cells
Tubulointerstitial Nephritis - Renal Failure

- Drugs or their metabolites act as haptens and bind to the tubular basement membrane or the interstitial matrix to form antigens
- A T-cell mediated delayed hypersensitivity reaction follows
- Patients may present with systemic manifestations of a hypersensitivity reaction such as fever, rash, and eosinophilia
- White blood cells and casts are frequently found in the urine
Tubulointerstitial Nephritis- Renal Failure

- Urinary casts are cylindrical structures produced by the kidney, all rely on the inclusion or adhesion of various elements on a mucoprotein base
- Cast describes the shape, so an adjective is added to describe the composition of the cast
- Cast formation is pronounced in environments favouring protein denaturation and precipitation (low flow, concentrated salts, low pH)

1 Acellular casts
   1.1 Hyaline casts
   1.2 Granular casts
   1.3 Waxy casts
   1.4 Fatty casts
   1.5 Pigment casts
   1.6 Crystal casts

2 Cellular casts
   2.1 Red blood cell casts
   2.2 White blood cell casts
   2.3 Bacterial casts
   2.4 Epithelial cell casts
Tubulointerstitial Nephritis - Renal Failure

Tubulointerstitial nephritis
- Antibiotics (penicillins, cephalosporins, sulphonamides, fluoroquinolones, rifampicin)
- NSAIDs
- Thiazide diuretics
- Lithium
- Proton-pump inhibitors
- Anti-epileptic drugs (phenytoin, valproic acid, carbamazepine)
- Allopurinol

Important clinical and laboratory findings:
- Sudden rise in creatinine
- Systemic manifestations of a hypersensitivity reaction: e.g., fever, rash and eosinophilia
- Urinary sediment: white blood cells (often eosinophils) and casts and proteinuria
Interstitial nephritis is a kidney disorder in which the spaces between the kidney tubules become swollen (inflamed).

Most often, interstitial nephritis is a short-term disorder. In rare cases, it can cause permanent damage, including chronic kidney failure.
Chronic Renal Failure

Chronic renal failure
Tubulointerstitial nephritis
  Lithium
  NSAIDs

Nephrotic syndrome
Glomerular disease
  NSAIDs
  Lithium
  Interferon α and β
  Pamidronate
  Sirolimus

Tubulopathies
Fanconi’s syndrome
  Tenofovir

Important clinical and laboratory findings:
Gradually declining renal function

Important clinical and laboratory findings:
Marked proteinuria, may be accompanied by haematuria and hypertension

Important clinical and laboratory findings:
Proteinuria, phosphaturia, glycosuria and bicarbonate wasting

Nephrotic syndrome – damage to the glomeruli, the kidneys' filtering system. This allows albumin to be filtered out into the urine (albuminuria)
Tenofovir Associated Renal Tubular Toxicity

- Tenofovir is a nucleotide reverse transcriptase antiretroviral
- The main site of toxicity being the proximal tubule
- Tenofovir - Fanconi’s syndrome is characterised by
  - Proteinuria
  - Phosphaturia
  - Glycosuria (with normal blood glucose)
  - Bicarbonate wasting [leading to metabolic acidosis]
    - glucose, amino acids, uric acid, phosphate and bicarbonate are passed into the urine, instead of being reabsorbed
- Risk factors or developing tenofovir-induced renal toxicity include
  - Pre-existing renal disease
  - Concomitant use of nephrotoxic drugs,
  - Low body weight and older age
- However, tenofovir-induced renal toxicity can occur in patients with no obvious risk factors
- It is important to monitor all patients on tenofovir treatment for renal dysfunction
Tenofovir Associated Renal Tubular Toxicity

- Increased urinary phosphate excretion has been associated with TDF use, and there is a theoretical concern regarding the potential effect of this on long-term bone density (analogous to the association between urinary calcium leak and bone demineralization).
- Fanconi syndrome
- Most likely within first 12 months but can be 5 years down the track
- Suggested alternate daily dosing when e-GFR <50mL/min
- Underdosing? Better to change therapy
Tenofovir Associated Renal Tubular Toxicity

- Acute tubular damage, with flattening of epithelia and interstitial oedema, and giant and misshapen mitochondria were seen in proximal tubule cells on electron microscopy, suggesting that mitochondria may be a target of TDF toxicity
- Tenofovir poisons mitochondria in the proximal tubular cell, therefore, energy source is removed and the transporters can no longer function
# Dolutegravir – Renal Failure?

<table>
<thead>
<tr>
<th>Adult Population</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Treatment-naïve</td>
<td>50 mg once daily</td>
</tr>
<tr>
<td><em>or</em> Treatment-experienced INSTI-naïve</td>
<td></td>
</tr>
<tr>
<td>Coadministered with potent UGT1A/CYP3A inducer:</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>50 mg twice daily</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Tipranavir/ritonavir</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>INSTI-experienced with certain INSTI mutations*</td>
<td></td>
</tr>
<tr>
<td><em>or</em> Clinically suspected INSTI resistance</td>
<td></td>
</tr>
<tr>
<td>Poor virologic response associated with Q148 Substitution plus ≥ 2 more INSTI mutations</td>
<td></td>
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INSTI = Integrate Strand Transfer Inhibitor
Creatinine

- A number of drugs from different therapeutic classes have been observed to reduce creatinine clearance without causing an effect on the rate of glomerular filtration.
- Decreases in creatinine clearance of 15–34 ml/min per 1.73m², have been noted with the antacid cimetidine, a number of antibiotics including trimethoprim and the antiparasitic pyrimethamine.
- Most recently, effects on serum creatinine increases of have been observed for the antiretroviral drugs rilpivirine and dolutegravir, and the pharmacoenhancers cobicistat and ritonavir.
Creatinine

- The effects on creatinine observed with these drugs have been attributed to the inhibition of the renal active tubular secretion component of creatinine clearance
Creatinine

- 80-90% of creatinine is filtered through the glomerulus (this is what makes up the GFR)
- In subjects with normal renal function, active tubular secretion accounts for 10–40% of creatinine clearance – Average of around 20-25%
Creatinine

- Dolutegravir and rilpivirine specifically blocks OCT2
- Also transports metformin excretion from the blood as well as creatinine
  - Unlikely pt will experience lactic acidosis (but be cautious) but likely increase in GIT side effects, possible in some patients might get better diabetic control
Creatinine

- After the age of 30 years, glomerular filtration rate (GFR) progressively declines
  - Average rate of 8 mL/min/1.73 m² per decade
- The Australian Diabetes, Obesity and Lifestyle (AusDiab) study suggests that over one-third of people over the age of 65 years have an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m²
- Therefore if serum Cr increases what is the baseline for elderly patients
Creatinine

• Polymorphism in transporters will have differences in % of Cr excreted

• Low expression or defect mutations in hOCT2 may reduce renal excretion of more hydrophilic cationic drugs, which may lead to increased hepatic elimination or toxicity
  – Are those with polymorphisms at increased risk of higher concentration of drugs like metformin in the blood at lower e-GFRs
### Creatinine

**IC50, half-maximal inhibitory concentration**

<table>
<thead>
<tr>
<th></th>
<th>OAT2</th>
<th>OCT2</th>
<th>OCT3</th>
<th>MATE1</th>
<th>MATE2-K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td>72.8±17.0</td>
<td>135±16</td>
<td>87.7±55.1</td>
<td>1.46±0.11</td>
<td>46.6±7.23</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>&gt;300</td>
<td>68.0±5.2</td>
<td>12.3±5.2</td>
<td>3.31±0.67</td>
<td>1.87±0.57</td>
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<tr>
<td>Cobicistat</td>
<td>&gt;100</td>
<td>24.0±4.6</td>
<td>&gt;100</td>
<td>1.87±0.22</td>
<td>33.5±4.2</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>&gt;20</td>
<td>~20</td>
<td>&gt;20</td>
<td>1.34±0.23</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>&gt;100</td>
<td>0.066±0.003</td>
<td>&gt;100</td>
<td>4.67±1.11</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
MINUTES TO MIDNIGHT: WHY THE QUAD IS A NO WIN FOR THE DRUG RESISTANT AND TREATMENT EXPERIENCED

01/15/2014  PANAWARE  LEAVE A COMMENT
Stribild

- **Tenofovir/emtricitabine/elvitegravir/cobicistat**
- Stribild was found to be non-inferior (of the same or slightly better efficacy) to Atripla
- Atripla and Stribild share an NRTI backbone and elvitegravir and raltegravir confer cross-resistance, patients who are resistant to Truvada and Atripla will also be resistant to Stribild
- Inability to safely use the drug to treat patients with creatinine clearances of less than 70mL/min and need to stop using it if creatinine clearance falls below 50 mL/min
- Increased creatinine levels and kidney damage have occurred, including cases of Fanconi syndrome and proximal tubular dysfunction
Stribild

- As the drug causes diarrhoea (reported by 22% of study participants taking Stribild), there is an increased risk of dehydration, which will exacerbate renal function if the volume depletion is severe enough and compound the issue of renal toxicity.
- The impairment in renal function is through to be associated with cobicistat. As a CTP3A4 and CYP2D6 inhibitor, there is significant potential for drug-drug interactions, enhancement of side effects.
Summary

• Drug-induced renal injury can be minimised by identifying high-risk patients and evaluating the nephrotoxic risk against the therapeutic benefit of administering the drug
  – Using gentamicin with vancomycin, dehydrated patients with drugs that could potentially reduce renal function

• Look at trends to evaluate baseline GFR with patients on medications that can increase creatinine but have no effect on GFR
  – No change in the glomerular filtration rate, as measured by iohexol clearance

• Getting the dose right can be extremely important for some medications
Summary

• Drugs like dolutegravir, corbicistat work via selective blockage not toxicity

• Blockage of OCT2 increases rapidly and then plateaus and becomes stable, therefore use baseline prior to this increase as the real e-GFR when dosing renally excreted doses

• Change from baseline Cr has a rapid increase about 10mL/min then (12 wks) stabilises, if renal function is not stabilising get concerned
Summary

- DTG not renally excreted, not renally toxic, no renal adjustment?
- Generally with DTG don’t use <50mL/min
- Corbicistat <70 mL/min
- NSAIDs are a tubular toxin (can also increase Cr) best to not use with tenofovir
- If serum Cr goes up with dolutegravir don’t have to stop, if it goes up with tenofovir you need to stop the tenofovir
Summary

- Serum k+ as well as trimethoprim on the same transporter, why at risk of hyperkalaemia
- Trimethoprim was found to reduce renal potassium excretion through the competitive inhibition of epithelial sodium channels in the distal nephron, in a manner identical to the potassium-sparing diuretic amiloride