Medications and the Nephron

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Objectives

• NSAIDs – Kidney Function, Potassium and Sodium
• Heparin - Potassium
• Sulfamethoxazole/Trimethoprim (Bactrim®) – Potassium and Creatinine
• Warfarin – Kidney Function
• Gout Medications and Kidney function
  - Certain medications and Uric Acid levels
**NSAIDs**

Non-steroidal anti-inflammatory drug

**PLEASE DO NOT TAKE**

- **Celecoxib** (Celebrex®)
- **Ibuprofen** (Advil®, Motrin®)
- **Indomethacin** (Indocin®)
- **Meloxicam** (Mobic®)
- **Naproxen** (Nasprosyn®, Aleve®, Anaprox®)
- **Diclofenac** (Voltaren®)
- **Sulindac**

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**Prostaglandin and thromboxane synthesis**
Non-steroidal Anti-inflammatory Drugs

NSAIDs

• COX-1
  – Expressed in most tissues
  – Regulates normal cellular processes

• COX-2
  – Expression increased during states of inflammation

NSAIDs and Renal Events

• Hemodynamic Kidney Injury
• Acute Interstitial Nephritis
• Nephrotic Syndrome
• Papillary Necrosis
• Electrolyte Abnormalities
• Hypertension/Edema
NSAIDs and Renal Events

- Occurs in 1-5% of NSAIDs users

- 2.5 Million incidents a year
  - ~ 70 million prescriptions
  - 30 billion OTC uses

- Risk Factors
  - Age
  - Hypercalcemia
  - Volume Depletion
  - Decrease Kidney perfusion form CHF, Nephrotic Syndrome or Cirrhosis
  - Medications specially ACEI and ARB
  - The above lead to increased production of COX-2

NSAIDs and Reducing GFR
NSAIDs and Hyperkalemia
NSAIDs and Hyperkalemia

50 hospital pts
Given Indomethacin
40%  K rose by 0.5 mEq/L
34%  K rose by 0.5-0.9 mEq/L
26%  K rose by 1 mEq/L

NSAIDs and Hyponatremia

- ADH is anti-diuretic hormone
- It increases the permeability of the collecting duct in the kidney for water retention when needed
- Produced in the Hypothalamus as response to Thirst, increase serum osmolarity and Hypovolemia
- Produced inappropriately in CHF and SIADH

NSAIDs and Hyperkalemia
**NSAIDs and Edema**

- Edema is due to Salt reabsorption
- PG contributes to Salt Wasting and Blocking their production ➔ Salt Retention
  - Studies showed 0.5-1 kg weight gain with chronic NSAIDs use
    - Effect most obvious in CHF and Cirrhosis
    - Resistance to Diuretics
  - PG cause vasodilatation and blocking its production ➔ vasoconstriction and increase in afterload in CHF
Which NSAIDs to Use?

• None if possible
• Some studies showed that Sulindac is the “safest’
• What about Aspirin?
  – Usually in low doses
  – Studies have shown that ASA has a Partial and Transient glomerular PG inhibition

Some NSAIDS Effects

In Summary

• Acute Kidney Injury
  – Hemodynamic AKI
  – Acute Interstitial Nephritis
  – Nephrotic changes in Minimal Change Disease and Membranous
• Hyperkalemia
• Hyponatremia
• Hypertension and Edema
Heparin and Hyperkalemia

• Even a prophylactic dose of 5000 BID SQ can lead to elevated Potassium
• This occurs in 7% of patients
• Severe Hyperkalemia in association with other factors like AKI, ACEI/ARB and Spironolactone
• Low Molecular Weight Heparin has the same effect
NSAIDs and Hyperkalemia

Heparin and Hyperkalemia
Sulfamethoxazole/Trimethoprim (Bactrim®)

TRIMETHOPRIM and HYPERKALEMIA
TRIMETHOPRIM and HYPERKALEMIA

• Dose Dependent
• Risk factors include:
  – The Elderly
  – Acute Kidney Injury
  – ACEI, ARB, NSAIDs or Spironolactone
• Typically, Potassium reaches 5 mEq/L in 4-5 days
TRIMETHOPRIM AND ELEVATED CREATININE

• Like many other drugs, it can cause Acute Interstitial Nephritis
• But ... that’s not what I am talking about here
NSAIDs and Hyperkalemia

Trimethoprim (in Bactrim®) and Elevated Creatinine

Serum Creatinine increases with no effect on GFR
WARFARIN AND KIDNEY INJURY

• Warfarin-related Nephropathy
• Acute Kidney Injury in patients on Warfarin (any anticoagulation) with a persistent INR >3-4
WARFARIN AND KIDNEY INJURY

• EPIDEMIOLOGY and ONSET
  – Usually occurs 8 weeks after initiation of Warfarin
  – Very difficult to assess the Epidemiology
  – Only confirmed by Biopsy that is performed less in such patients
    • Reluctance to biopsy patients with high INRs
    • AKI is attributed to other Etiologies
  – Approximately 17% of patients experience WRN and the percentage increases with the presence of certain risk factors

WARFARIN AND KIDNEY INJURY

• RISK FACTORS
  – Chronic kidney disease
  – Heart disease
  – Hypovolemia
  – Glomerulonephritis
  – Hypertension
PRESENTATION OF WRN

• 8 weeks into the initiation of Warfarin
• Patients are Hypertensive, volume overloaded with decreased UOP
• Rarely with Gross Hematuria and mainly microscopic hematuria
  – Absence of Hematuria does not exclude WRN
TREATMENT & PROGNOSIS OF WRN

• Reversal of hypercoagulation
  – Quick reversal might be of benefit
• Supportive care
• Most patients improve their Creatinine within
  the first few weeks of normalized INR
  – Some patients continue to have CKD and actually
  some studies showed increase Mortality

WARFARIN-RELATED NEPHROPATHY

• AKI in pts on Warfarin (or Dabigatran) usually
  for 8 weeks with INRs >3-4 leading to
  Glomerular bleeding and RBC cast (with or
  without M. Hematuria) that usually resolves
  with cessation of Warfarin and reversal of
  anticoagulation with the usual recommended
  management
GOUT and Kidney

GOUT TREATMENT in CKD

• 98% of Gout patients, in General, are undertreated
Purine → Hypo-Xanthine → Xanthine → Uric acid → Allantoin

- Beer x2-4
- Liquor x1-2
- Red Meat, Sea Food

- Xanthine Oxidase
- Uricase in other Mammals

- 10,000 Patents
- OTC Cosmetics
- Smothes Skin
- Wound Healing
- Anti Irritant

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Allopurinol Dose

- Approved for a dose up to 800 mg a day (key is to keep Uric acid levels <6 mg/dL)
- Can be given in Chronic Kidney Disease
- Not removed by Dialysis
- Allopurinol → Oxypurinol (a Xanthine Oxidase Inhibitor and accumulates in Renal Failure)
  - $\text{CrCl} 10-20 \rightarrow 200 \text{mg of Allopurinol daily}$
  - $\text{CrCl} 3-10 \rightarrow 100 \text{mg of Allopurinol daily}$
- Watch out when given with Azathioprine

Allopurinol and Azathioprin
Allopurinol and Febuxostat
Structurally Different

Febuxostat Dose

• No adjustment needed for CrCl > 30 mL/min
• Not well defined for CrCl < 30
Colchicine

- Helps with making the Diagnosis
- For those who cannot tolerate NSAIDs
- Key is to start within 12-24 hrs
- Do not give it IV
- Two dosing regimens
  - High dose: 6 x 0.6 mg over 5 hours (Side Effects)
  - Low dose: 1.2 mg immediately and 0.6 mg an hour later (then 0.6 mg QD or BID until 2 days after complete resolution of Pain)

Colchicine in Renal Failure

- For Acute Attacks
  - CKD: No adjustment especially if using the low (1.8 mg/day)
  - HD: Not recommended as Colchicine cannot be removed on HD
GOUT MEDECINE DOSING

• **Allopurinol** up to 800 mg/day
  – uric acid goal is <6 mg/dL

• Careful with Azathiprine

• Kidney Failure
  – Minimal adjustment in CrCl >20
  – CrCl <20 → 200 mg
  – CrCl <10 → 100 mg

• Allopurinol and Febuxostat have different Structures

HYPERURICEMIA and DIURETICS
HYPERURICEMIA

• Goal is to keep Uric acid <6
• One of the most common causes of Hyperuricemia is Diuretics

Diuretics and Hyperuricemia

• **Loops Diuretics** and **Thiazides** confer the same risk of Hyperuricemia and Gout (Dose-dependant)

• **Potassium-sparing Diuretics** do not have a similar risk

• Do not need to stop Diuretics

• Start Gout medications when indicated
HYPERURICEMIA and LOSARTAN

• One trick is to use Losartan along with Diuretics

• Angiotensin II blockade in general will, in theory, lead to Uricosuria

• However, Losartan, has a Direct Uricosuric effect and seems to be the only ARB that does that

Hyperuricemia and Losartan

• 2 Randomized Trials:
  - 1161 pts w HTN were randomly assigned to Losartan (UA decreased), Candesartan (UA stayed the same), or Losartan + HCTZ (UA increased). After 12 weeks. (Manolis 2000)
  - Compared Losartan w/ Enalapril.
    No other metabolic differences (Tikkanen 2001)

• Another small prospective study. Losartan and not Irbesartan, decreased serum uric acid levels by 9 % at 4 weeks. (Würzner 2001)
MISCILENIUS HYPERURICOSURIC DRUGS

- Other common Uricosuric drugs:
  - Fenofibrate
  - Calcium Channel Blockers

- Beta Blockers contributes to Hyperuricemia

DIURETICS AND HYPERURICMIA

- Diuretics
  - Hyperuricemia with HCTZ, Lasix (but Not Spironolactone) and Beta Blockers

- Losartan, Fenofibrate and CCB lower Uric acid Levels
Bibliography


Bibliography