CRRT: Difficult ICU Problems
Electolyte and Acid-Base Disorders

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Case 1

- A 60 year-old male with a history of a heart transplant and stage 4 chronic kidney disease was diagnosed with a gout flare 6 days ago and was prescribed prednisone 30 mg daily, allopurinol 100 mg daily along with colchicine 0.6 mg tid for the first two days and then 0.6 mg bid after that. Prior to the gout attack, the patient had been feeling well and his baseline creatinine was 2.9 mg/dl with an estimated glomerular filtration rate (eGFR) of 29 ml/min/1.73m^2. Other medications included: mycophenolate mofetil, cyclosporine, pravastatin, carvedilol, calcitriol and furosemide.

Case 1

- After 48 hours of taking the allopurinol, colchicine and prednisone, the patient developed nausea, intermittent vomiting and profuse diarrhea. This continued intermittently over the next 2 days. However, over the past 2 days, he has developed worsening lethargy, muscle aches and continued nausea, diarrhea and abdominal pain. His family brings him to the emergency department (ED).

- In the ED, he was found to be confused, tachycardic and hypotensive with a blood pressure of 76/42 mmHg and pulse of 120/minute. He then suffered a respiratory arrest and was successfully intubated as well as started on vasopressin, norepinephrine and intravenous fluids to support his blood pressure. Laboratory results at the time of admission revealed the following:

Case 1

- Sodium 130 meq/L
- Potassium 2.5 meq/L
- Bicarbonate 6 meq/L
- Chloride 108 meq/L
- Blood Urea Nitrogen 101 mg/dL
- Glucose 101 mg/dL
- Creatinine 6.9 mg/dL
- Creatine phosphokinase (CPK) 12,000 IU/L
- Troponin 0.2 ng/ml
- AST 198 IU/L
- ALT 100 IU/L
- Albumin 3.7 g/dL

- White blood cell 1200 cells/mm^3
- Hemoglobin 11 g/dL

- Arterial blood gas:
- pH 6.91
- pCO_2 23
- pO_2 75

Case 1: Question 1a

- The acid-base abnormality in this patient is:

  A. Anion gap and non-anion gap acidosis

  B. Respiratory acidosis and anion gap acidosis

  C. Respiratory alkalosis and anion gap acidosis

  D. Respiratory acidosis and anion gap and non- anion gap acidosis

  E. Respiratory alkalosis and anion gap and non- anion gap acidosis

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Discussion

Acid-base analysis

1. Acidemia (pH 6.91)
2. Metabolic acidosis (bicarbonate is 6)
3. Anion gap: 130-108-6 = 16 (albumin is nl)
4. Expected pCO2

   Winter's Formula: Expected $pCO_2 = 1.5 * HCO_3^- + 8 +/- 2$

   Expected pCO2 = 1.5 (6) + 8 = 17 +/- 2 (15-19)

   Actual pCO2 = 23, so concomitant respiratory acidosis

Discussion

Does it fit with clinical picture?

Diarrhea: non-gap acidosis

Volume depletion: hypoperfusion and lactic acidosis

Respiratory muscle weakness, CNS depression: resp acidosis

-Anion gap = 16

Normal bicarbonate = 24

Expected bicarbonate if all AG = 22

Thus, there is a small non-anion gap acidosis

METABOLIC ACIDOSIS: gap and non-gap acidosis

RESPIRATORY ACIDOSIS

Case 1: Question 1b

- Which of the following drug interactions were likely responsible for the patient's presentation?

  A. Allopurinol, pravastatin and mycophenolate mofetil

  B. Allopurinol, pravastatin and cyclosporine

  C. Colchicine, allopurinol and mycophenolate mofetil

  D. Colchicine, pravastatin and cyclosporine

  E. Colchicine, prednisone and pravastatin

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  B. Allopurinol, pravastatin and cyclosporine

  C. Colchicine, allopurinol and mycophenolate mofetil

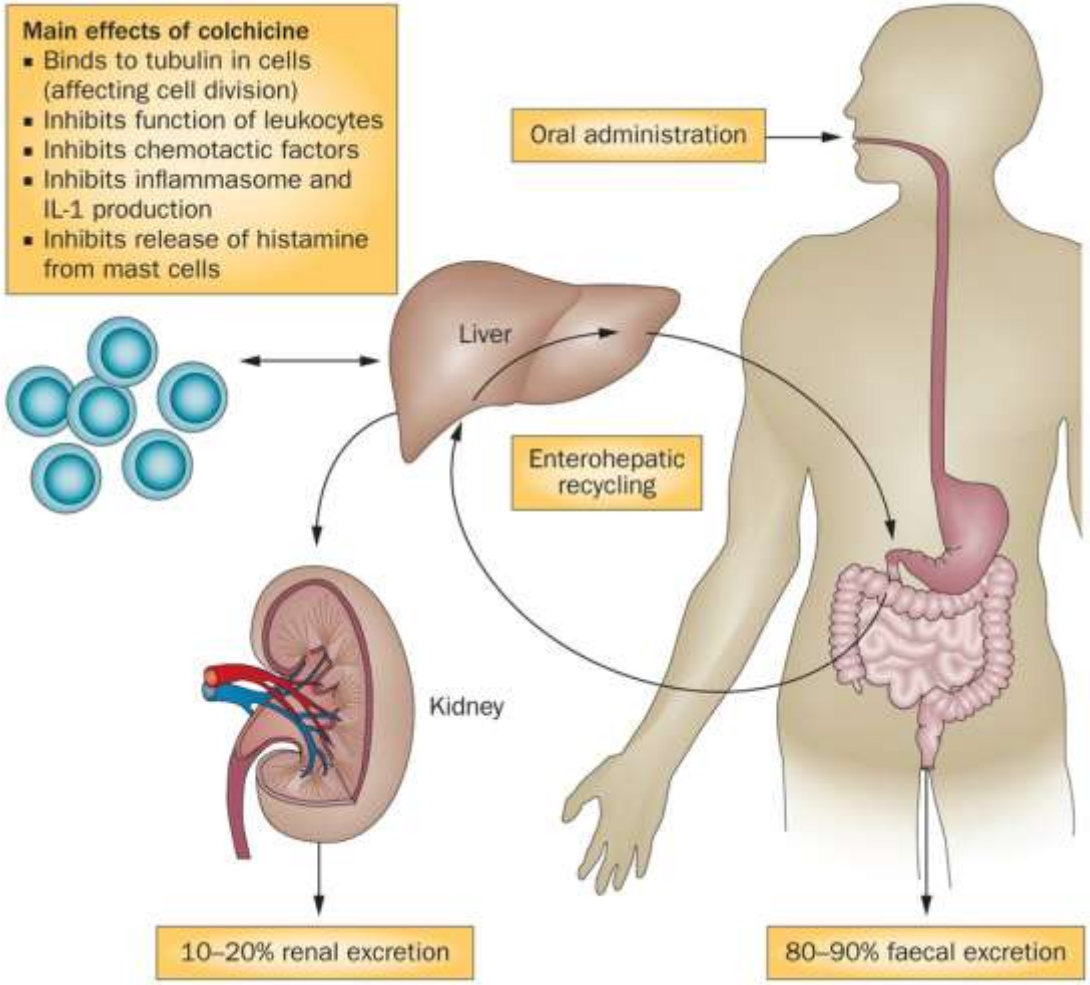
  D. **Colchicine, pravastatin and cyclosporine**

  E. Colchicine, prednisone and pravastatin

Colchicine Poisoning

- Colchicine is a widely prescribed and effective medication for the treatment of gouty arthritis.
- Plants such as autumn crocus or meadow saffron (*Colchicum autumnale*) and glory lily (*gloriosa superba*) contain colchicine alkaloids.
- Colchicine is a mitotic inhibitor that terminates cell division and is thought to have an anti-inflammatory effect as an inhibitor of leukocyte migration and the secretion of inflammatory glycoproteins

Colchicine Poisoning



Nature Reviews Rheumatology 10, 271–283 (2014)

Acute Intoxication

- Fatal dose is 0.8 mg/kg
- Stage 1 (10-24 hours post-ingestion): largely gastrointestinal symptoms
- Stage 2 (24h to 7 days): multisystem organ failure (bone marrow suppression, liver injury, rhabdomyolysis, ARDS, cardiogenic shock)
- Stage 3 (variable, weeks): recovery
- Death is usually associated with cardiogenic shock, ARDS and multi-system organ failure
- Survival is dependent upon dose ingested, arrival time to hospital after ingestion and rapid therapy of lactic acidosis (often requires hemodialysis)
- Case reports of ECMO use also suggest benefit in severe circumstances

Ther Clin Risk Manag 2013; 9: 505-9
Intensive Care Med 2013; 39: 1163

The Kidney and Colchicine

- Toxicity more common with underlying CKD due to renal excretion (10-20%)
- Acute kidney injury
  - Not due to a direct toxic effect of colchicine
  - Usually associated with multi-system organ failure, volume depletion, rhabdomyolysis and concomitant ingestions (such as NSAIDS)
- Electrolyte abnormalities
  - Hypokalemia, hypomagnesemia, hypophosphatemia are common and most likely due to diarrhea and vomiting
  - One report of a Fanconi-like syndrome
  - Severe metabolic acidosis (lactate)

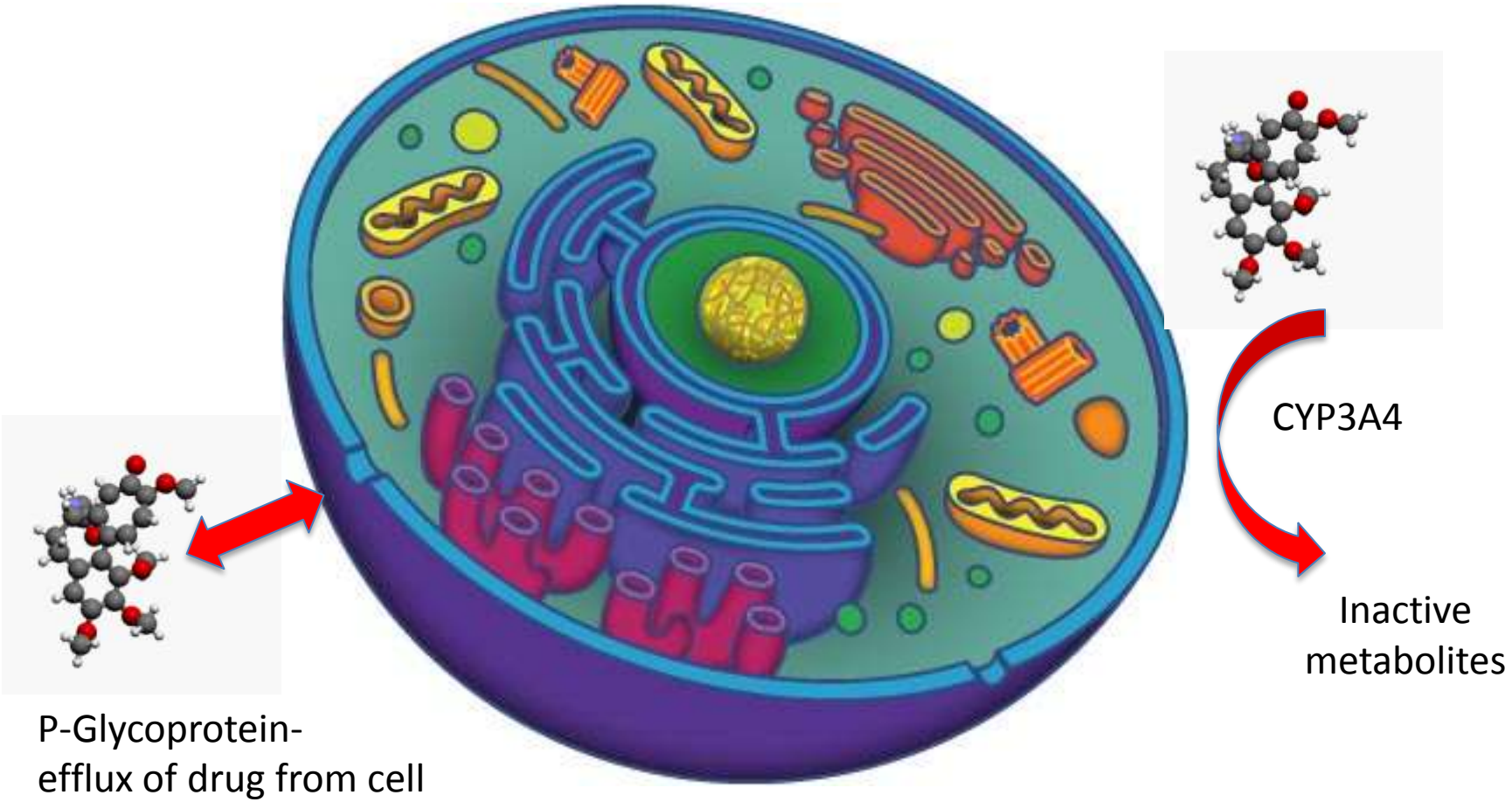
Int J Clin Pharmacol Ther 2005; 43: 480-4
Ren Fail 2007; 29: 367-370

Drug Metabolism and Interactions

- Metabolized by CYP3A4
  - Colchicine levels significantly increased by:
    - Clarithromycin, Azithromycin
    - Ketoconazole, itraconazole, fluconazole
    - Cyclosporine (single case report with tacrolimus)
    - Grapefruit juice
- Efflux from cells through P-glycoprotein
  - Toxicity enhanced by blocking this pathway leading to higher intracellular levels
    - Statins (associated with high-risk of rhabdomyolysis)
    - Cyclosporine

Clin Toxicol 2008; 46: 827-830
Transplant Proc 2012; 44: 2851-2

Colchicine Metabolism



Colchicine and Cyclosporine

- Effect of cyclosporine (100-mg capsule) on the pharmacokinetics of colchicine (0.6-mg tablet) after single oral-dose administration
- Increased colchicine maximum observed plasma concentration, and area under the plasma concentration-time curve to time infinity on average by 224% and 215% (ie, almost doubled), respectively
- Decreased colchicine oral clearance on average by 72% (from 48.24 to 13.42 L/h), indicating substantially higher colchicine exposures when combined with cyclosporine, compared with colchicine alone
- Recommended to decrease colchicine dose $\geq$ 50%

Postgrad Med 2012; 124: 189-196

Therapy of Colchicine Poisoning

- Although charcoal is potentially beneficial in preventing colchicine absorption and significant enterohepatic recirculation, it is of limited utility due to rapid and excellent absorption of colchicine
- Due to colchicine's extensive volume of distribution and excellent tissue binding, hemodialysis and hemoperfusion do not effectively remove the drug and are not recommended unless used as a supportive measure for patients in renal failure or with severe acidosis.
- Case reports of using plasma exchange suggest benefit

Clin Toxicol 2011; 49: 739-743

Therapy of Colchicine Poisoning

- Aggressive supportive care is critical in the management of colchicine poisoned patients.
- Early fluid resuscitation and correction of electrolyte abnormalities are essential.
- Ventilator support and blood product transfusions are often needed in the patient severely poisoned by colchicine.
- Patients who develop bone marrow suppression should be placed on neutropenic precautions. Colony stimulating factors such as G-CSF have been used for the treatment of colchicine-induced leukopenia.
- In Europe, an experimental colchicine Fab antibody solution was used to treat patients with severe colchicine poisoning, however, this product is not currently commercially available in Europe or the United States.

Case #2

- A 37 year-old female with a 3 year history of severe sinus disease and headaches is referred to you secondary to the finding of several laboratory abnormalities. Her past medical history is significant for two episodes of nephrolithiasis (no stone analysis was performed). On questioning she notes that pain and redness develops in her hands in cold weather. She takes no medications except for occasional antibiotics for her sinus problems. Her blood pressure is 108/50 mmHg and her physical examination is unremarkable with the exception of some fullness over her parotid glands. The following labs are sent from her primary care physician:

Case #2- Laboratory

- Sodium 141 meq/L
- Potassium 2.9 meq/L
- Bicarbonate 11 meq/L
- Chloride 125 meq/L
- Calcium 9.0 mg/dL
- Phosphorus 3.1 mg/dL
- Magnesium 1.7 mg/dL
- Albumin 3.7 g/dL
- Total protein 8.5 g/dL
- Blood Urea Nitrogen 18 mg/dL
- Glucose 80 mg/dL
- Creatinine 1.3 mg/dL

- On further questioning, she denies any drug abuse. Repeat labs in your office confirm the past values and in addition, the following urine chemistries are obtained:

- Urine pH 6.5
- Urine sodium 38 meq/L
- Urine potassium 45 meq/L
- Urine chloride 20 meq/L

Case 2: Question 2a

- Which one of the following laboratory tests would you order next?

  A. Serum and urine protein electrophoresis

  B. Plasma renin and aldosterone levels

  C. 24 hour urine cortisol

  D. Stool screen for laxative abuse

  E. Anti-SSA, Anti-SSB serologies

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AG 5

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- Urine pH 6.5 ↑
- Urine sodium 38 meq/L
- Urine potassium 45 meq/L ↑
- Urine chloride 20 meq/L

Urine Anion Gap = (83-20) +63

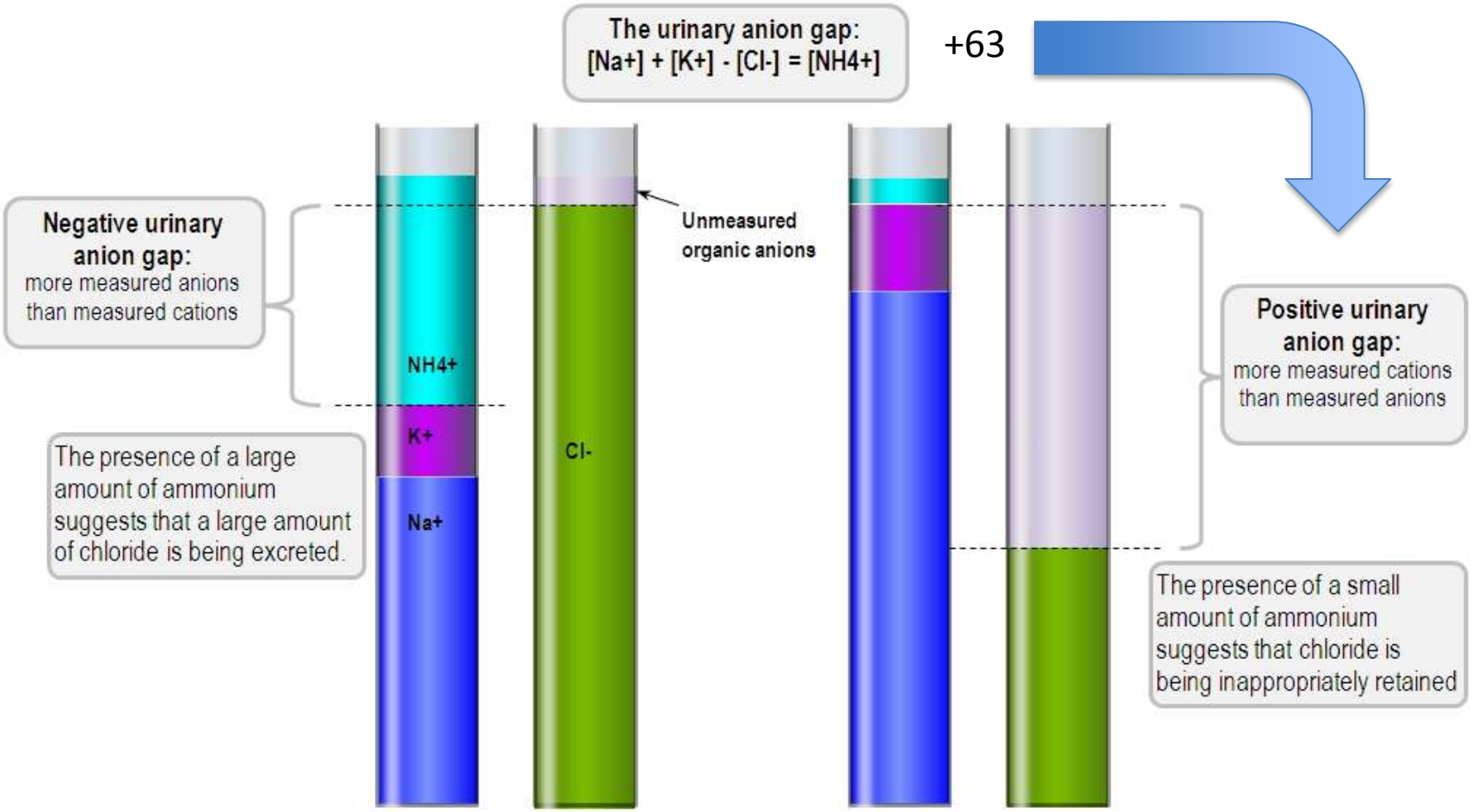
Non Anion Gap Acidosis

- Normal or high K+
  - Administration of HCl or precursors
  - Administration of cationic amino acids
  - Chronic kidney disease
  - Adrenal insufficiency
  - Hyporeninemic hypoaldosteronism
  - Hyperkalemic distal RTA
  - Pseudoaldosteronism type I
  - Pseudoaldosteronism type II (Gordon's syndrome)
  - Drugs (spironolactone, prostaglandin inhibitors, triamterene, amiloride, trimethoprim, pentamidine, cyclosporine

- Low K+
  - Diarrhea
  - Intestinal fistulae
  - Proximal RTA
  - Distal RTA
  - Uterosigmoidostomy
  - Ureteroileostomy
  - Diabetic ketoacidosis*
  - Toluene intoxication*
  - d-Lactic acidosis*

*Can have a high anion gap, a normal anion gap or a mixed pattern

Urinary Anion Gap



Distal Renal Tubular Acidosis

- Characteristic features
  - Systemic Acidosis
  - Inability to acidify the urine pH < 5.3
- Associated with many diseases

- Four groups:

1. Voltage Defect
2. H+ Secretion Defect
3. H+ Gradient Defect
4. Ammonium Generation Defect

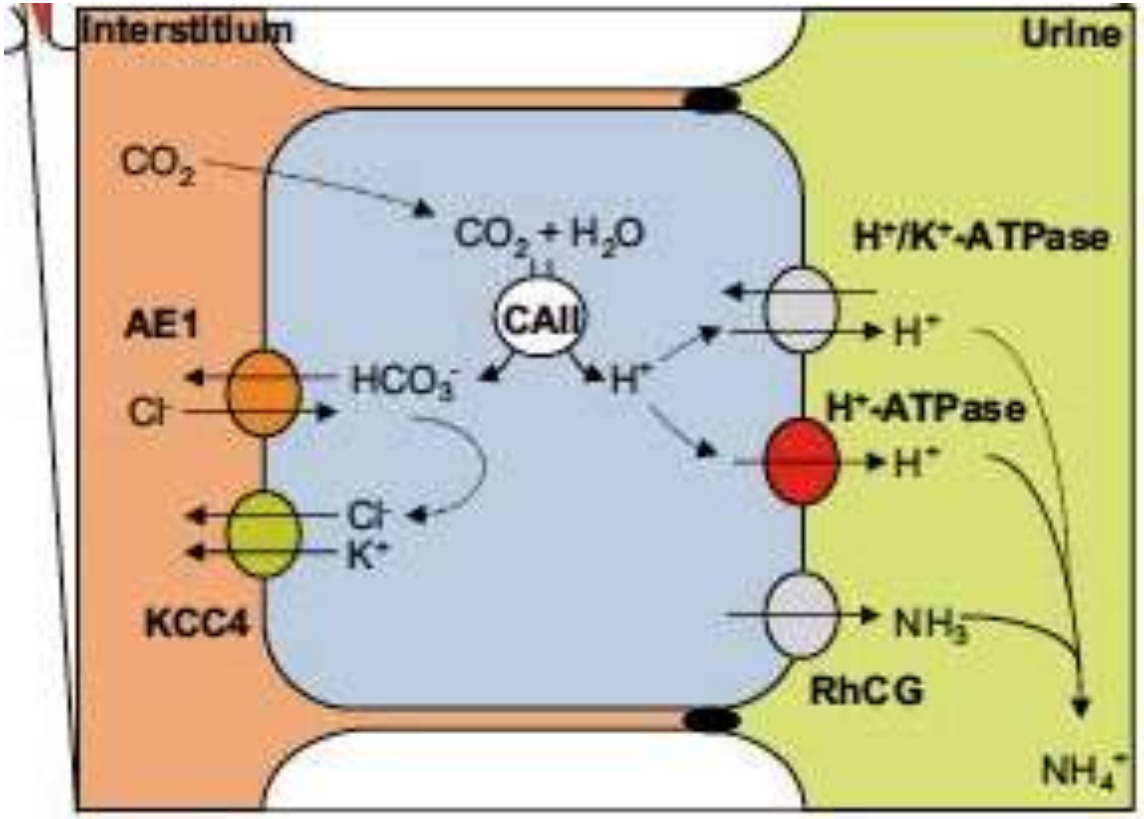
Voltage Defect-dRTA

- Electronegative potential in the collecting tubule contributes to H+ secretion
- Primarily driven by ENaC's reabsorption of sodium
- Regulated by aldosterone

- Genetic Causes
  - Mutations in ENaC: Autosomal recessive pseudohypoaldosteronism
  - α unit (SCNN1A)
  - β unit (SCNN1B)
  - γ unit (SCNN1C)
  - Mineralocorticoid receptor defect (NR3C2): Aut Dom
- Acquired Causes
  - Hyporeninemia (diabetes)
  - Drugs (amiloride, calcineurin inhibitors, ACE-inhibitors, ARBs, heparin)

H+ Secretion Defect

α-Intercalated cells



Mutations in:

1. H+ ATPase (AR +/- deafness)
2. AE1 (AD)
3. CA II (proximal and distal RTA)
4. Medullary sponge kidney

Acquired:

1. Autoimmune diseases (Sjogren's and SLE)- against CAII
2. Medications:
   topiramiate
   acetazolamide

H+ Gradient Defect

- Proton secretion is dependent upon the H+ gradient over the apical membrane established by the vacuolar H+ ATPasee
- Creation of the gradient can be impaired if the plasma membrane is leaky as seen with amphotericin B
- Amphotericin B increases the membrane permeability for H+ leading to back diffusion

Douglas JB, Healy JK. Am J Med 1969; 46: 154-162

Ammonium Secretion Defects (Hyperkalemia)

- A low availability of ammonium limits acid excretion
- Most important cause of decreased urinary ammonium is hyperkalemia which reduces the expression of ammoniagenic enzymes
- Also decreases the secretion of ammonium in the loop of Henle and collecting duct through competitive binding between K+ and NH4+
- Also drives H+ extracellularly leading to a decreased concentration of H+ in the distal tubular cells

Karet FE. J Am Soc Nephrol 2009; 20: 251-254

Hypokalemia in dRTA

- Most likely due to the **H+ secretion defect**
- Wasting of potassium in the urine is due to the need to maintain electroneutrality over the apical membrane
- Potassium levels are highly variable and can be normal
  - Maintained by systemic acidemia
- Patients with autoimmune disease-induced dRTA tend to have hypokalemia due to inhibition of carbonic anhydrase II.
  - Leads to more profound bicarbonate and potassium wasting

Conner DM, et al. Ann Clin Biochem 2008; 45(part 2): 221-225

Nephrolithiasis in dRTA

- Metabolic acidosis: exchanges H+ for sodium, potassium, calcium, carbonate and phosphate in bone
- Also stimulates osteoclast development and activity and leads to bone loss and hypercalciuria
- Metabolic acidosis also leads to enhances proximal tubular reabsorption of citrate
- Alkaline urine in combination with hypocitraturia, hyperphosphaturia and hypercalcuria leads to calcium phosphate stones and/or nephrocalcinosis

Krieger NS et al. Curr Opin Nephrol Hypertens 2004; 13: 423-436
Both T, et al Rheumatol Int 2014; 34: 1037-1045

dRTA and Autoimmune Diseases

- Overt dRTA is seen in 3-5% of patients with Sjogren's Syndrome (can also be seen in other disorders but much less frequently)
- However, up to 25-35% may have some defect in acid secretion (incomplete dRTA)
- Largest study of 130 patients with Sjogren's and renal involvement:
  - 95 patients developed an RTA
  - 91 with dRTA (66 complete and 25 incomplete)
  - 4 with pRTA and Fanconi Syndrome
  - 9 patients presented with hypokalemia paralysis

Petrovaara M, et al. Rheumatology 1999; 38: 1113-1120
Ren H, et al. J Rheumatology 2008; 35: 278-284

Mechanism of dRTA in Sjogren Syndrome

- Unclear
- Immune mediated damage to acid secreting cells is likely
  - Several studies demonstrating absence of the vacuolar H+ ATPase as well as absence of anion exchanger 1 (AE1)
  - Newer studies: elevated antibody levels to carbonic anhydrase II
  - Intriguing finding is that mice ingested with human CAII develop a syndrome similar to Sjogren Syndrome
  - Diffuse tubulointerstitial disease as well
- Not clear that immunosuppressive therapy aids dRTA

Defranco PE, et al. J Am Soc Nephrol 1995; 6: 295-301
Cohen EP et al. J Am Soc Nephrol 1992l 3: 264-271
Takemoto F, et al. Am J Med 2005; 118: 181-184

Answer

- Distal RTA- can be confirmed by rapid urinary acidification test with furosemide 40 mg and fludrocortisone 1 mg were controls will acidify the urine pH < 5.3 and dRTA will not be able to do this
- However, the finding of a low bicarbonate and a urine pH > 5.3 establishes the diagnosis of dRTA
- Sjogren Syndrome- diagnosed by clinical symptoms and confirmed by serologies (anti-SSA/SSB)

Walsh SB et al. Kidney Int 2007; 71:1310-1316

Case 2: Question 2b

- Aggressive intravenous potassium chloride and oral potassium citrate supplementation are administered. Repeat labs one week later reveal the following: potassium 3.5 mEq/L; bicarbonate 15 mEq/L, and anion gap 6. The patient is seen by a neurologist for her chronic headaches and topiramate 200 mg daily is started.

- Which of the following changes would be expected if laboratory work was repeated several weeks after starting topiramate?

A. Potassium 2 meq/L; Bicarbonate 5 meq/L; Anion gap 8
B. Potassium 4 meq/L; Bicarbonate 20 meq/L; Anion gap 8
C. Potassium 4 meq/L; Bicarbonate 5 meq/L; Anion gap 15
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E. No change in electrolytes from prior values

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Topirimate

- Topirimate is approved for seizure prevention and migraine prophylaxis (as well as numerous off-label uses)
- Observations early on demonstrated that topirimate was associated with a non-gap metabolic acidosis and increased incidence of calcium phosphate kidney stones

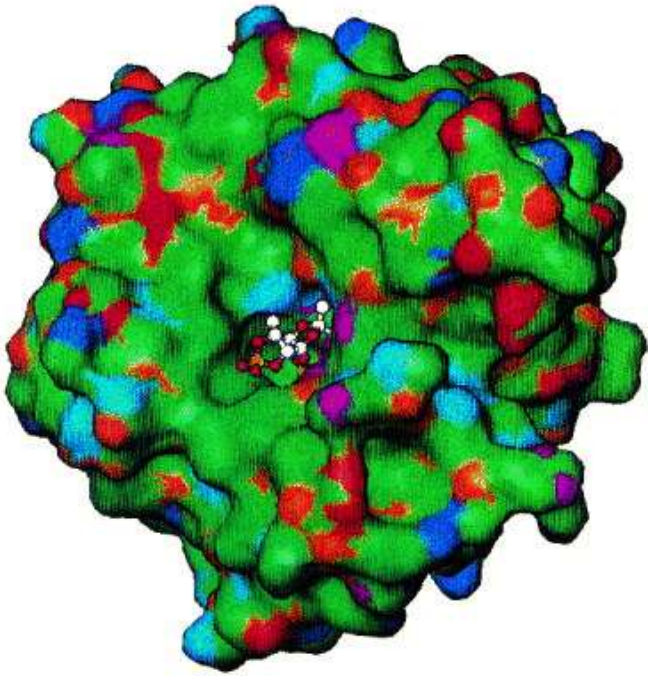
Dodgson SJ et al. Epilepsia 2000; 41(suppl1): S35-39

Topirimate and Metabolic Acidosis

- In clinical trials, 32% of patients treated with topirimate developed a serum bicarbonate < 20 meq/L as compared with 1% of placebo treated patients
- On average, bicarbonate levels fell 5 meq/L once starting topirimate
- Uncommonly, bicarbonate levels fell to < 10 meq/L
- Acidosis is associated with alkaline urine, positive urine anion gap and low urine citrate

Garris SS, et al. Ann Pharmacother 2005; 39: 424-426
Welch BJ et al. Am J Kidney Dis. 2006; 48: 555-563
Mizra N et al. Br J Clin Pharmacol 2009; 68:655-661

Topirimate and Carbonic Anhydrase



Topirimate binding to catalytic site of CAII

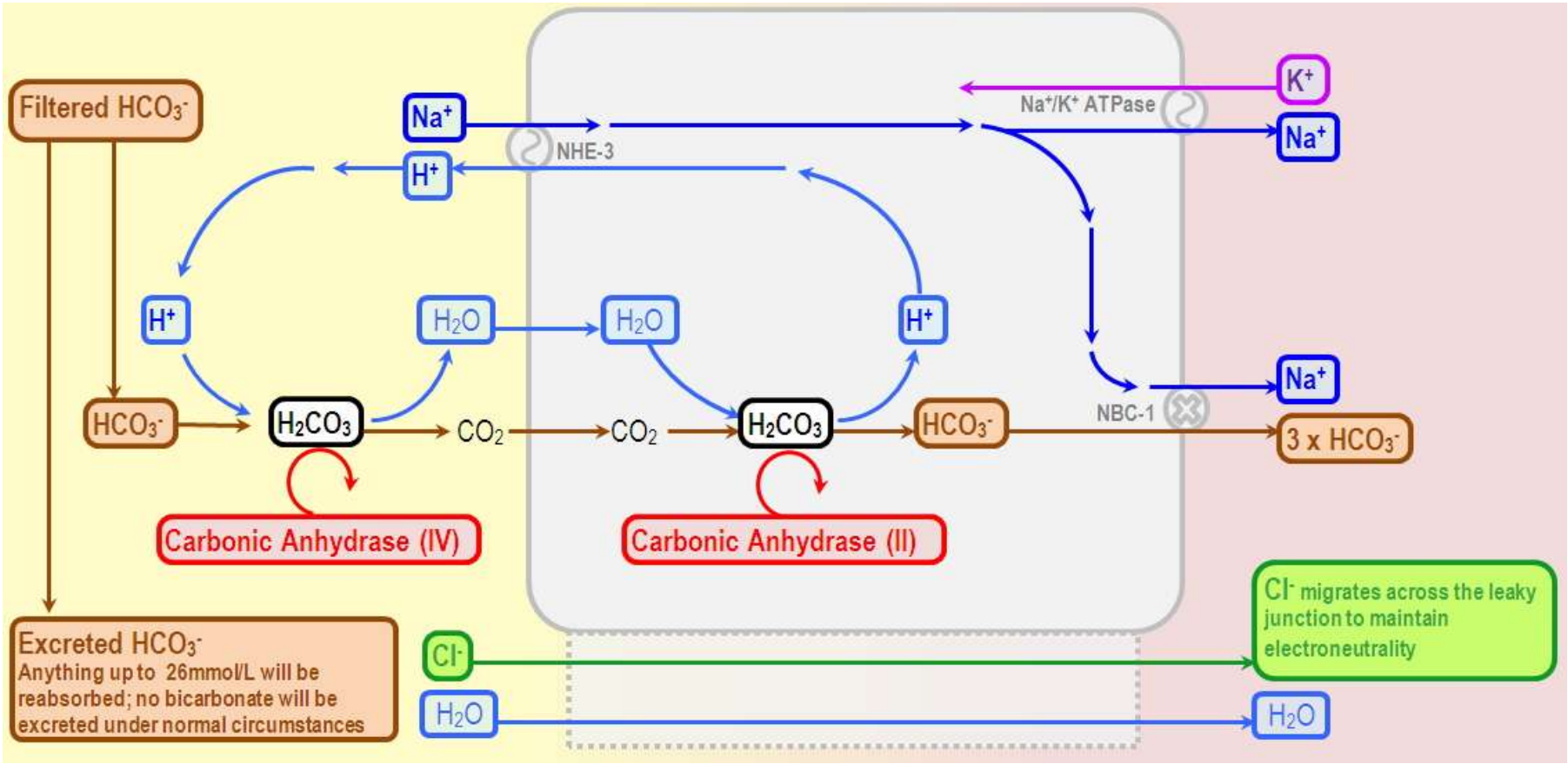
Topirimate is an inhibitor of carbonic anhydrase with preferential inhibition of CAII isoenzyme

Acetazolamide is 10-100x more potent inhibitor of CA

Rechacha R et al. Biochem J 2002; 361: 437-441

Carbonic Anhydrase

Isoenzyme CAII present in both proximal and distal tubule and mutations lead to mixed proximal and distal RTA (seen mostly in the middle East and North Africa)



Summary

- Topirimate caused worsening non-gap acidosis in a patient with Sjogren Syndrome due to inhibition of both proximal and distal acidification mechanisms.
- Hypokalemia is likely due to excessive bicarbonate in the distal tubule which obligates increased potassium excretion +/- contribution of hyperaldosteronism (sodium depletion with excess bicarbonate loss)