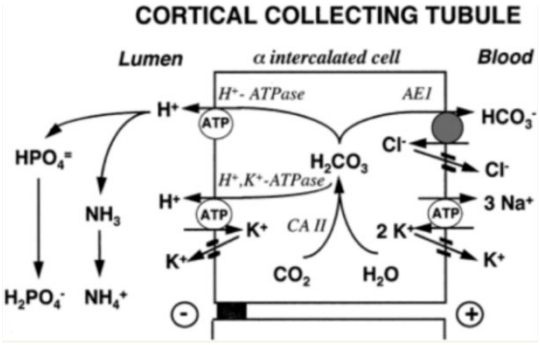
Clinical Pharmacology & Toxicology Pearl of the Week

~ Drug Induced Renal Tubular Acidosis ~

Background

- ✓ The kidneys play an important role in maintaining acid-base homeostasis, resorbing filtered bicarbonate and removing excess hydrogen ions. When these mechanisms fail, a renal tubular acidosis (RTA) can occur. There are many drugs that can play a role in the development of an RTA.

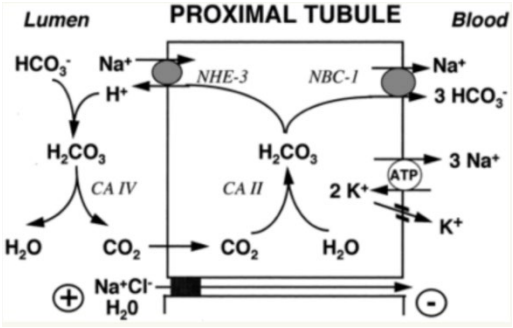
Distal RTA



Distal Acidification of Urine **Soriano JR. Renal Tubular Acidosis: The Clinical Entity. JASN. 2002**

- ✓ Distal RTA is characterized by impairment of H^+ secretion by the distal nephron, which results in reduced NH_4^+ excretion.
- ✓ Amphotericin B: Induces RTA type 1 by increasing membrane permeability in the collecting duct, and results in back-diffusion of secreted H^+ ions and K^+ wasting.
- ✓ Foscarnet: The mechanism is thought to relate to mitochondrial dysfunction leading injury to the renal tubule cells.
- ✓ Lithium: It has been hypothesized that lithium administration induces distal renal tubular acidosis by allowing excessive back-diffusion of acid.

Proximal RTA



Proximal Reabsorption of Bicarbonate **Soriano JR. Renal Tubular Acidosis: The Clinical Entity. JASN. 2002**

- ✓ The proximal tubule plays an important part in acid base balance by reclaiming filtered bicarbonate. This happens via multiple steps:
    - First, carbon dioxide enters across the apical membrane.
    - The second process is apical H^+ secretion via Na-H exchange and H^+ pumping
    - Next, there is basolateral exit of HCO_3^- via the electrogenic Na/HCO_3 cotransporter
    - The final step is regulation of overall HCO_3^- reabsorption by CO_2 and HCO_3^- sensors at the basolateral membrane.

When proximal tubule function becomes impaired, the result is bicarbonaturia and metabolic acidosis. There are multiple medications that can impair these pathways.

- ✓ Carbonic anhydrase inhibitors: These drugs include acetazolamide, dorzolamide and methazolamide. The defect in bicarbonate reabsorption with CA inhibitors can be explained by inhibition of CA IV located in the apical membrane of the proximal tubule cell resulting in the isolated inhibition of bicarbonate reabsorption.
- ✓ Ifosfamide: An alkylating agent which is used in the treatment of various cancers such as bone sarcomas, soft tissue sarcomas and testicular cancer. The mechanism by which ifosfamide causes renal tubular damage is not completely understood.
- ✓ Cisplatin: Toxicity is caused by a direct toxic effect on the amino acid transporter in the proximal convoluted tubule causing a renal fanconi syndrome, and induces cell apoptosis.
- ✓ HIV Medications (Tenofovir), valproic acid, aminoglycosides and tetracyclines: Induce proximal tubule dysfunction via effects on mitochondria.

Type 4 RTA

- ✓ The pathophysiology of a type 4 RTA involves generation of hyperkalemia resulting in increased competition for the potassium-ammonium transport at the thick ascending limb of the nephron. Decreased ammonium reabsorption results in decreased medullary ammonium concentration and decreased ammonium secretion in the collecting duct, and increased chloride reabsorption ultimately leading to a non-anion gap metabolic acidosis. Deficiencies in aldosterone are an important pathway to which potassium is retained and sodium excreted, which can lead to conditions that drive the above pathway.
- ✓ Multiple medications can play a role in the generation of a type 4 RTA:
    - Diminished renin secretion: NSAIDS
    - Diminished ACE activity: ACE inhibitors
    - ACE receptor inhibition: Angiotensin-II receptor blockers, LMWH
    - Diminished aldosterone secretion: NSAIDS
    - Diminished aldosterone receptor function: Calcineurin inhibitors (cyclosporin, tacrolimus), Aldosterone receptor blockers (spironolactone, eplerenone)
    - Decreased ENaC channel function: Amiloride, triamterene, trimethoprim, pentamidine

	RTA-1 (Generalized distal)	RTA-2 (Proximal)	RTA-4 (Aldosterone resistance or deficiency)
Lab findings			
Typical severity of acidosis	Bicarb ~10-20 mM	Bicarb ~12-20 mM	Mild (Bicarb >17 mM)
Potassium	↓↓	↓	↑ (often primary manifestation)
Other electrolytes		In generalized prox tubule dysfunx: ↓ Ca, ↓ Mg, ↓ Phos, ↓ Uric acid	
Glucosuria	-	+	-
Urine pH[1]	>5.3	Variable	Usually <5.5
Urine osmolar gap	< 150 mOsm	>150 mOsm	< 150 mOsm
Causes			
Medications	Amphotericin NSAIDs Lithium Ifosfamide Foscarnet	Carbonic anhydrase inhibitors - Acetazolamide - Topiramate - Mafenide acetate Generalized defect - Aminoglycosides - Tenofovir, anti-retrovirals - Valproic acid - Chemotherapeutics (e.g. platinum agents, Ifosfamide)	Trimethoprim, pentamidine Amiloride, triamterene Spironolactone, eplerenone ACE-i, ARB, renin inhibitors NSAIDs, beta-blockers Cyclosporine, tacrolimus Heparin
Genetic disorders	Wilson's disease Sickle cell anemia Ehlers-Danlos, Marfan's	Wilson's disease	Sickle cell anemia

https://emcrit.org/ibcc/nagma/

References

Pham AQ, Xu LH, Moe OW. Drug-Induced Metabolic Acidosis. *F1000Res*. 2015;4:F1000 Faculty Rev-1460. Published 2015 Dec 16. doi:10.12688/f1000research.7006.1

Nascimento L, Rademacher DR, Hamburger R, Arruda JA, Kurtzman A. On the mechanism of lithium-induced renal tubular acidosis. J Lab Clin Med. 1977 Mar;89(3):455-62. PMID: 839104.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-cal physician is listed in ROCA. Clinical Pharmacology consultations are also available through Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

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 1-866-1212 (SK).