Renal Tubular Acidosis: A Drug-Centric Perspective

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v. 3.3 NOV 2014. updates at www.peterloewen.com

Presence of non-anion gap hyperchloremic metabolic acidosis

- leflunomide, ifosfamide, oxaliplatin, deferasirox, acetazolamide, aminoglycosides, cyclosporine, tacrolimus, adefovir/tenofovir/cidofovir, didanosine / lamivudine / stavudine, 5-ASA, coumarin, Streptozocin, tetracyclines, Valproic acid
- analgesic overuse, toluene, vitamin D intox, Foscarnet, phenytoin, phenobarbital, topiaramate, zonisamide, ibuprofen
- amphotericin B
- lithium
- triamterene, amiloride, trimethoprim
- spironolactone, eplerenone, NSAIDs, ACE-inhibitor, long-term heparin

Type 3 now considered a severe form of Type 1 or a mix of Type 1 & 2.

Type 2 RTA (proximal RTA, pRTA)?

decreased bicarb resabsorption in proximal tubule (threshold >15)

Features:
-UAG NEGATIVE
-usually moderate, self-limiting met.acidosis
-urine pH<5.5 when serum bicarb drops near 15 mmol/L
-normo or hypokalemia

Non-drug causes:
Primary, hereditary, sporadic, decreased carbonic anhydrase activity/CA deficiency, genetic diseases (**Fanconi syndrome**, tyrosinemia, Wilson's disease, glycogen storage disease, galactosemia, ARC Syndrome, Alport syndrome), multiple myeloma, amyloidosis, nephrotic syndrome, hypocalcemia, vit.D deficiency / resistance, **Sjogren's syndrome**, renal vein thrombosis, renal transplant rejection, lead / cadmium / mercury toxicity, hyperparathyroidism, medullary cystic kidney disease

Therapy if primary, drug can't be stopped or short-term therapy needed:
-often none
-high dose oral alkali (4-20 mmol/kg/d bicarb). (see bottom left for quantities)
-+/- thiazide diuretic + low Na diet
-K+ supp may be needed

Type 1 RTA (distal RTA, dRTA)?

Don't forget about NH3 synthesis/transfer defect!:
Features: urine pH<5.5, normokalemia

secretory defect "classical RTA"

- rate-limited defect -?defective H+ pump
  - Features:
    -UAG POSITIVE
    -urine pH<5.5
    -milder form of gradient-type?
    -hypokalemia in 30-50% of cases, otherwise normokalemic
    -may be "incomplete" defect and only uncovered during illness or acid load
- gradient limited defect -? absent H+ pump
  - Features:
    -UAG POSITIVE
    -urine pH>5.5
    -hypokalemia in 30-50% of cases, otherwise normokalemic

Non-drug causes:
-Primary (sporadic [eg. sepsis], hereditary, a.k.a "incomplete RTA")
-Genetic (Marfan's syndrome, sickle-cell disease, elliptocytosis, medullary cystic disease, Fabry's disease, Wilson's disease, Ehlers-Danlos syndrome, osteopetrosis)
-**Autoimmune** (Sjogren's syndrome, SLE, RA, vasculitis, hypergammaglobulinemia, chronic active hepatitis, primary biliary cirrhosis, thyroiditis, fibrosing alveolitis)
-Calcium problems (idiopathic hypercalciuria, hyperparathyroidism, medullary sponge kidney)
-chronic pyelonephritis, renal transplant, hepatic cirrhosis, amyloidosis, vanadate

permeabillity defect

? back-diffusion of H+ out of tubule

Features:
-UAG POSITIVE
-urine pH >5.5
-possible hypokalemia

Non-drug causes: NONE

voltage-dependant defect

lack of lumen electronegativity d/t decreased cortical Na + reabsorption

Features:
-UAG POSITIVE
-urine pH>5.5
-hyperkalemia

Non-drug causes: avid salt retention

Therapy if primary, drug can't be stopped or short-term therapy needed:
-Initially to correct acidosis: calculate bicarb required (based on total body bicarb deficit) and give 1/3-1/2 IV over 4-8 hours. Give remainder over >24 hours (eg. infusion at ~2 mEq/kg/d) as Na-bicarb or K-bicarb
-Chronic therapy: PO bicarb 0.5-2 mEq/kg/d in 2-4 doses as baking soda (mixed in water or diet soda) or Na or K citrate solution (Dicitrate). (see bottom left for quantities)
-supplement K+ if hypokalemic (K-bicarb or K-citrate)
-use furosemide if volume overload or renal insufficiency is a problem

Type 4 RTA?

Hyperkalemia causes ↓ NH3 synthesis → ↓ ability to acidify urine.

Features:
-hyperkalemia
-urine ph<5.5 when acidemic

Non-drug causes:
renin deficiency, **primary hypoaldosteronism**, aldosterone resistant states, SLE(?)

Therapy if primary, drug can't be stopped or short-term therapy needed:
-furosemide
-K+ restriction
-low-dose PO bicarb (1-2 mEq/kg/d) (see bottom left for quantities)
-fludrocortisone 50-200 mcg/d

Goals of therapy:
1. prevent nephrocalcinosis, osteomalacia, rickets
2. prevent severe acidosis, respiratory failure & death
3. prevent hypokalemic paralysis (with rhabdomyolysis), hyperkalemia & death
4. prevent irreversible renal damage (if drug-induced)
5. prevent fatigue

NOTES:
-> UAG = urine (Na + K) - urine Cl
-> urine pH must be measured promptly (it increases as it sits since CO_2 evaporates & bacteria produce urease -> increased urea… can't run pH on previously obtained sample)
-> most labs measure pH in 0.5 increments and only if >5.5
-> urine Cl- is hard to do (not all labs can do it)

Alkali Replacement:
-> Total body bicarb deficit (mEq)= (desired - actual) x 0.6 x wt
-> Baking soda contains 12 mEq bicarb/g and ~270 mg Na+/g
-> K-citrate & Na-citrate (Dicitrate) contain 1mEq bicarb/mL (+ 1mEq K+ or Na+ per mL)
->NaBicarb tablets contain 325mg NaBicarb (=4 mEq bicarb + 90 mg Na+/ tablet)

RENAL TUBULAR ACIDOSIS COMPARISON TABLE

Type	Metabolic acidosis?	Anion gap	Serum Cl-†	Serum K+*	UAG**	Urine pH
pRTA (Type 2)	✓	Normal	↑	Normal	NEG	<5.5 when acidemic
dRTA (Type 1)						
-NH_3 synth / transport defect	✓	Normal	↑	Normal	POS	<5.5
-secretory defect	✓	Normal	↑	↓ in 30-50% of cases	POS	>5.5 (if gradient-limited, <5.5 if rate-limited)
-permeability defect	✓	Normal	↑	↓ usually	POS	>5.5
-voltage defect	✓	Normal	↑	↑	POS	>5.5
Type 4	✓	Normal	↑	↑	POS	<5.5 when acidemic

†currently thought to be due to overactive Cl-/HCO3- exchange pump in distal tubule (in Type1) [Pediatr Nephrol 2006;21:206-211]
*when corrected for acidosis (eg. pH Δ 0.1 ~ K+ Δ 0.6 mmol/L)
**UAG = urine (Na + K) – Cl