Clinical aspects of renal tubular acidosis

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acidosis:

Is it real?
$H^+ + HCO_3^- \rightleftharpoons \text{H}_2\text{O} + \text{CO}_2$
What do you need to assess an acid-base disorder

- Blood: blood gas, electrolytes including bicarbonate (measured)
- Urine: ph, electrolytes
- The bicarbonate (or base excess) on a gas is calculated => less reliable
Then you just look it up!
Renal tubular acidosis

- Acid-base homoeostasis is maintained by the kidney
- Excretion of acid should be equal to acid ingested (acid load)
Renal Acid Load

Depends on diet:

- Animal proteins are high in sulfur-containing AA (cystine, methionine) and thus acid-producing.
- Vegetable fruit, tubers, roots and leafy green vegetables contain salts of organic acids, which are metabolised to bicarbonate.
- Typical western diet presents a net acid load of ~50 mmol to the kidney.
Renal Bicarbonate Handling

• In order to excrete acid, the kidney first needs to reclaim the filtered $\text{HCO}_3^-$
• Approximately 4 Mol of $\text{HCO}_3^-$ is filtered each day
• 80-90 % is reclaimed in proximal tubule
• 10-20 % in distal nephron
Proximal tubule

CA2

NHE3/SLC9A3

CA4

NBCe1/SLC4A4

Proximal tubule cell

Lumen

Blood

CO₂ + OH⁻ → HCO₃⁻

H₂CO₃ → H⁺ + CO₃²⁻

HCO₃⁻ + H⁺ → CO₂ + OH⁻

Glucose, Amino acids, Phosphate

Na⁺, K⁺
Distal Tubule

**Principal cell**
- $K^+$
- $2K^+$
- $3Na^+$
- Na-K-ATPase
- ENaC
- ROMK

**α-Intercalated cell (CCT & MCT)**
- ATP1A4
- ATP1B1
- H^+
- CO$_2$
- HCO$_3^-$
- OH^-
- CA2
- AE1/SLC4A1
And now to the clinical approach

P H<7.37, HCO₃⁻ <20

- **Anion gap**
  - **normal**
  - **high**

- **Intestinal Bicarbonate losses**
  - yes
  - no

- **Diarrhoea? GI-fistula? Stoma?**
  - yes
  - no

- **Urine pH**
  - <5.5
  - ≥6.5

- **Glucosuria? Aaciduria? Low TmP?**
  - yes
  - no

- **Serum K⁺**
  - high
  - low

- **Fanconi Syndrome**
  - yes
  - no

- **Isolated pRTA invalid data**
  - yes
  - no

- **Inherited dRTA**

- **Methanol**
- **Uraemia**
- **DKA**
- **Paraldehyde**
- **Iron**
- **Lactate**
- **Ethylene glycol/Ethanol**
- **Salicylic acid**

- **Hyperkalaemic RTA**
- **Aldosterone insufficiency/resistance**
- **Renal failure**
- **Obstructive uropathy**
The anion gap

- $\text{Na}^+ - \left[\text{Cl}^- + \text{HCO}_3^-\right] = \text{AG}$
- Normal: 8-12
What is the anion gap

- Unmeasured anions, mostly proteins
- Therefore: in hypoalbuminaemia expect low anion gap
- Correction: anion gap decreases by 2.5 for each 10g/l of serum albumin below 40 g/l
Renal tubular acidosis = non-anion gap acidosis

• Non-anion gap = bicarbonate loss
• Bicarbonate is lost through gastrointestinal tract (diarrhoea) or the kidney (RTA)
• Because of electroneutrality, bicarbonate loss must be accompanied by cation loss, typically sodium

\[ \text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-] = \text{AG} \]
The difference between anion gap and non-anion gap acidosis

• Anion gap = acid gain.
• Addition of acid, where the corresponding base is an unmeasured anion, such as lactate or ketones.
• Thus, the added proton is buffered by bicarbonate, decreasing the serum level, but the added anion is unmeasured.

\[ \text{Na}^+ - [\text{Cl}^- + \text{HCO}_3^-] = AG \]
Clinical consequences of renal tubular acidosis

- Failure-to-thrive
- Protons replace calcium ions in the bone, resulting in
  - Rickets
  - Hypercalciuria/nephrocalcinosis
Case 1

• 6 weeks old baby referred for failure to thrive. Born FT with a birth weight of 3.22 kg.
• Failed newborn hearing screen
• Examination: weight 3.0 kg, otherwise unremarkable
# Laboratory Investigations

<table>
<thead>
<tr>
<th>Blood</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na 147 mmol/l</td>
<td>Na 60 mmol/l</td>
</tr>
<tr>
<td>K 2.3 mmol/l</td>
<td>K 36 mmol/l</td>
</tr>
<tr>
<td>Cl 127 mmol/l</td>
<td>Cl 62 mmol/l</td>
</tr>
<tr>
<td>HCO₃ 10 mmol/l</td>
<td>pH 8.0</td>
</tr>
<tr>
<td>pH 7.20</td>
<td></td>
</tr>
</tbody>
</table>
Renal Ultrasound
pH=7.20, $\text{HCO}_3^-$ = 10

↓

Anion gap

$AG = 147 - (127 + 10) = 10 = \text{normal}$
pH<7.37, $\text{HCO}_3^-$ <20

Diarrhoea? GI-fistula? Stoma?

normal Anion gap
Urine pH = 8.0

- pH < 7.37, $\text{HCO}_3^- < 20$
- Anion gap normal
- Diarrhoea? GI-fistula? Stoma? no

Urine pH = 8.0
K = 2.3 mmol/l

pH < 7.37, HCO₃⁻ < 20

Anion gap

Diarrhoea? GI-fistula? Stoma? normal

no

Urine pH

≥ 6.5

Serum K⁺
pH<7.37, HCO$_3^-$ <20

Anion gap

Diarrhoea? GI-fistula? Stoma? normal

Urine pH

Serum K$^+$

≥6.5

low

Inherited dRTA
Distal Tubule

- **Principal cell**
  - MRCR
  - ENaC
  - Na-K-ATPase

- **K⁺**
  - ROMK

- **Na⁺**
  - ATPV0A4
  - ATPV1B1
  - AE1/SLC4A1

- **3Na⁺**

Diagram showing the flow of ions and transport proteins in the distal tubule.
Case 2

- A 7 day old baby is brought to the A&E department because of weight loss, vomiting and being listless. Birth weight was 2.75 kg and on admission she weighs 2.32 kg with poor perfusion and unmeasurable blood pressure.
Laboratory Investigations

- **Blood**
  - Na: 126 mmol/l
  - K: 8.8 mmol/l
  - Cl: 107 mmol/l
  - HCO$_3^-$: 10 mmol/l
  - pH: 7.16

- **Urine**
  - Na: 196 mmol/l
  - K: <1 mmol/l
  - Cl: 168 mmol/l
  - pH: 7.5
pH=7.20, HCO_3^- = 10

\[ \text{Anion gap} \]

\[ AG = 126 - (107 + 10) = 11 = \text{normal} \]
pH<7.37, HCO₃⁻ <20

Diarrhoea? GI-fistula? Stoma?

Anion gap

normal
Urine pH = 7.5

pH < 7.37, HCO₃⁻ < 20

Anion gap

normal

Diarrhoea? GI-fistula? Stoma?

no

Urine pH

Urine pH = 7.5
pH < 7.37, $\text{HCO}_3^- < 20$

- Diarrhoea? GI-fistula? Stoma? normal no
- Urine pH $\geq 6.5$
- Serum $K^+$

$K = 8.8 \text{ mmol/l}$
pH<7.37, HCO$_3^-$ <20

Diarrhoea? GI-fistula? Stoma?

Anion gap

Serum K$^+$

Urine pH

>6.5

Hyperkalaemic RTA
Aldosterone insufficiency/resistance
Renal failure
Obstructive uropathy
Distal Tubule

Principal cell

- 2K⁺
- 3Na⁺
- Na-K-ATPase

K⁺

MCRB

BNaC

Na⁺

ATP0A4

ATP1B1

CA2

AE1/SLC4A1

H⁺

OH⁻

CO₂

H₂O

Cl⁻

Na⁺

Lumen

α Intercalated cell (CCT & MCT)

Na⁺

Blood

CO₂

HCO₃⁻
Case 3

- A 2-year old boy is brought to clinic because of failure to thrive. His weight has fallen below the 0.4th percentile.
- His examination is remarkable for widening of chosto-chondral junctions and wrists.
# Laboratory Investigations

- **Blood**
  - Na: 137 mmol/l
  - K: 2.6 mmol/l
  - Cl: 110 mmol/l
  - HCO\(_3\): 14 mmol/l
  - pH: 7.24

- **Urine**
  - Na: 24 mmol/l
  - K: 13 mmol/l
  - Cl: <50 mmol/l
  - pH: 6.0
pH=7.20, $\text{HCO}_3^-$ = 10

$\text{AG} = 137 - (110 + 14) = 13 = ?$ normal
pH<7.37, HCO₃⁻ <20

Diarrhoea? GI-fistula? Stoma?

normal

Anion gap
Urine pH = 6.0

pH<7.37, HCO_3^- <20

Diarrhoea?  GI-fistula?  Stoma?
(normal)

Anion gap

no

Urine pH

<5.5  >6.5

Urine pH = 6.0
Diarrhoea? GI-fistula? Stoma?

normal

no

Urine pH

<5.5 Glucosuria? Aaciduria? Low TmP?

yes

Fanconi Syndrome

pH<7.37, HCO$_3^-$ <20

Anion gap

≥6.5

TRP: 58% (↓)
(TmP/GFR: 0.56)
Urine RBP: ↑↑↑
+glucosuria
Case 4

• A 1–year old girl is referred to clinic because of her family history of dominant dRTA (mother and maternal grandmother). She has been well, thriving and developing.

• Her examination is unremarkable (height and weight on the second percentile).
# Laboratory Investigations

- **Blood**
  - Na: 144 mmol/l
  - K: 4.3 mmol/l
  - Cl: 108 mmol/l
  - $\text{HCO}_3$: 20 mmol/l
  - pH: 7.34

- **Urine**
  - Na: 14 mmol/l
  - K: 54 mmol/l
  - Cl: 45 mmol/l
  - pH: 7.5

- **Calcium/creatinine ratio**: 0.36 (0.07 - 1.5)
Ultrasound
Is she affected?
Follow-up

• Admitted locally age 17 months with diarrhoea and found to have low plasma bicarbonate (15 mmol)

• Seen again in clinic age 18 month

• Blood
  Na  140 mmol/l
  K   4.2 mmol/l
  Cl  108 mmol/l
  HCO₃ 16 mmol/l
  pH  7.29

• Urine
  Na  47 mmol/l
  K   191 mmol/l
  Cl  100 mmol/l
  pH  7.5

• Calcium/creatinine ratio 0.34 (0.07 - 1.5)
Time for questions!