Anion Gap Metabolic Acidosis

ASN BRCU 2014
Michael Emmett MD

Henderson-Hasselbalch Equation

\[
\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \]

\(\text{(Renal-Metabolic)}\)

\(\text{H}_2\text{CO}_3 = (0.03)\text{pCO}_2\)

\(\text{pCO}_2\)

\(\text{pH} = 6.1 + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \)

\(\text{(Pulmonary)}\)

\[\text{pCO}_2 = \text{HCO}_3^- + 15\]

\[\text{pCO}_2 = 1.5(\text{HCO}_3^-) + 8 (\pm/2)\]

Metabolic Acidosis & Respiratory Alkalosis
(pCO₂ is relatively too low)

\[\text{pCO}_2 = 1.5(\text{HCO}_3^-) + 8 (\pm/2)\]

Winter’s Equation

James L. Gamble
(1883–1956) “Gamblegrams”

THE ANION GAP

ANIONS - CATIONS AND THE ANION GAP

\[\text{AG} = [\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)]\]

10 +/- 2 mEq/L Old

8 +/- 2 mEq/L New

ANION GAP METABOLIC ACIDOSIS

\[\text{AG} = [\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)]\]

25 mEq NaHCO₃
105 mEq NaCl
10 mEq NaAG

15 mEq NaHCO₃
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10 mEq NaAG

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**ANION GAP METABOLIC ACIDOSIS**

**M-U-D-P-I-L-E-S**

- Ketosis – β-OH-Butyric & Acetoacetic Acid
- Uremia – Multiple organic & Inorganic acids
- Salicylate – Multiple Organic Acids
- Methanol – Formic Acid
- Aldehydes – Acetic Acid
- Lactate – L-Lactic Acid
- Ethylene Glycol – Glyoxylic & Oxalic Acid
- D-Lactic Acid
- Propylene Glycol – D & L Lactic Acid
- Diethylene Glycol
- 5-Oxoproline (Pyroglutamic Acid)

**Ketosis** – β-OH-Butyric & Acetoacetic Acid

**Uremia** – Multiple organic & Inorganic acids

**Salicylate** – Multiple Organic Acids

**Methanol** – Formic Acid

**Aldehydes** – Acetic Acid

**Lactate** – L-Lactic Acid

**Ethylene Glycol** – Glyoxylic & Oxalic Acid

**D-Lactic Acid**

**Propylene Glycol** – D & L Lactic Acid

**Diethylene Glycol**

**5-Oxoproline (Pyroglutamic Acid)**

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**Boston Approach**

pH, pCO₂, HCO₃⁻, Anion Gap

William Schwartz & Arnold Relman

Donald Seldin; Michael Emmett

Most Nephrologists & Internists Especially in USA

**Copenhagen Approach**

pH, pCO₂, Base Excess

Poul Astrup; Ole Siggaard-Andersen; Niels Fogh-Andersen; John Severinghaus

Many Anesthesiologists & Surgeons

**Stewart Method**

pCO₂, Sb, AₒT

Peter Stewart; Vladimir Fencl; John A. Kellum

David Storey; Howard Corey

Many Anesthesiologists and Intensivists

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**HUMAN ALBUMIN**

At pH = 7.4

about net 16 negative charges

MW = 66,500 mg/mm

1 gm% = 0.154 mm/l

For each 1 gm% fall in albumin the AG falls

~ 2.5 - 3 mEq/l

AG adjusted = AG + 3 (4.5-observed Alb)

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68 yo man with 3 days high fevers, dysuria and weakness. BP is 90/70; pulse 110/min.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>125 mg%</td>
</tr>
<tr>
<td>BUN</td>
<td>26 mg%</td>
</tr>
<tr>
<td>Cr</td>
<td>1.1 mg%</td>
</tr>
</tbody>
</table>

Δ = 10 mEq/l
68 yo man with 3 days high fevers, dysuria and weakness. BP is 90/70 with pulse 110/min.

\[
\begin{align*}
\Delta &= 10 \text{ mEq/l} \\
\text{Glucose} &= 125 \text{ mg\%} \\
\text{BUN} &= 26 \text{ mg\%} \\
\text{Cr} &= 1.1 \text{ mg\%} \\
\text{Albumin} &= 2.1 \text{ gm/100ml} \\
3 \times 2.5 &= 7.0 \\
\therefore \text{Corrected AG} &= 17 \\
\text{Lactate} &= 8 \text{ mEq/l}
\end{align*}
\]
**Ethylene Glycol**

**Definitive Rx**
- Inhibit Alcohol Dehydrogenase
  - Fomepizole or Ethanol
- Hemodialysis
  - Removes EG and toxic metabolic products
- Indications: Severe AG metabolic acidosis (pH < 7.2), worsening acidosis despite fomepizole Rx, serum EG level > 50 mg/dl, renal failure, severe electrolyte abnormalities
  - Continue until the serum EG is < 10 mg/dl, or until asymptomatic + acidosis resolved.
  - Fomepizole probably allows Rx without HD absent severe metabolic acidosis & renal failure

**Criteria for Initiation of Rx in Patients with Ethylene Glycol Poisoning**
- Plasma concentration ≥20 mg/100ml (3.2 mmol/liter)
- Documented recent history of ingestion of toxic amounts of ethylene glycol & osmolal gap >10 mOsm/l
- Suspected ethylene glycol ingestion and at least three of the following:
  - Arterial pH <7.3
  - Serum HCO3 <20 mmol/l
  - Osmolal gap >10 mOsm/l
  - Oxalate crystalluria

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**Relative Affinity for ADH**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Affinity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antizol</td>
<td>8000</td>
</tr>
<tr>
<td>Ethanol</td>
<td>1</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.065</td>
</tr>
<tr>
<td>Ethylene Glycol</td>
<td>0.015</td>
</tr>
</tbody>
</table>

**Loading**
- Load with 15 mg/kg then 10 mg/kg q 12 hr X 4 doses then 15 mg/kg q 12 hr (i.e. about 1 gm initially for a 70 kg patient)
- During HD administer q 4 hr
- 1.5 ml vial (1gm/ml). Dilute & infuse over 30 min.
- Now Generic Cost: about $800/vial ($ 400-550/dose)

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**Bicarbonate**
- Temporizing measure for severe metabolic acidosis (pH < 7.2)

**Thiamine**
- Conversion of glyoxylic acid to less toxic α-OH ketoadipate
  - (100 mg IV qd to qid)

**Pyridoxine**
- Facilitates conversion of oxalic acid to glycine
  - 50 - 100 mg qd to qid

**Gastric lavage**
- Generally of little utility because EG very rapidly absorbed
- Use only if very large ingestion within 30 - 60 minutes

**Activated charcoal**
- Little value because EG poorly absorbed to charcoal
- Use if co-ingestants are suspected

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**Unproven or of no Value**

- Bicarbonate
- Thiamine
- Pyridoxine
- Gastric lavage
- Activated charcoal

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**ETHYLENE GLYCOL Rx**

- Bicarbonate
- Thiamine
- Pyridoxine
- Gastric lavage
- Activated charcoal

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**American Academy of Clinical Toxicology practice guidelines**

J Toxicol Clin Toxicol 1999;37:537
55 y.o. man with long standing history of alcohol abuse is hospitalized with acute pancreatitis. His condition deteriorates and he is transferred to the ICU. On the 3rd hospital day he develops delirium tremens. His chemistries at this time include: Glucose 110 mg%; BUN 35 mg%; Creatinine 2.2 mg%

Treatment includes D5% NS, multivitamins, thiamine. IV lorazepam is started and the dose is titrated up to control his agitation. The dose is stabilized at 0.15 mg/kg/hr (~10 mg/hr)

Two days later he is doing much better in general but his chemistries reveal:

<table>
<thead>
<tr>
<th>Glucose</th>
<th>BUN</th>
<th>Cr</th>
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<tbody>
<tr>
<td>138 mg%</td>
<td>40 mg%</td>
<td>3.0 mg%</td>
</tr>
</tbody>
</table>

Osmolality = 320 mOsm/l
PROPYLENE GLYCOL (Racemic L&D)

LACTALDEHYDE (L&D)

D+L - LACTIC ACID

METHYLGLYOXAL


Commonly used intravenous drugs containing propylene glycol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amount of Propylene Glycol (% v/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam, 2 mg/mL</td>
<td>80</td>
</tr>
<tr>
<td>Phenobarbital, 30–130 mg/mL</td>
<td>68–75</td>
</tr>
<tr>
<td>Diazepam, 5 mg/mL</td>
<td>40</td>
</tr>
<tr>
<td>Pentobarbital, 50 mg/mL</td>
<td>20–40</td>
</tr>
<tr>
<td>Phenytoin, 50 mg/mL</td>
<td>40</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole (16:80)</td>
<td>40</td>
</tr>
<tr>
<td>Etorphate, 2 mg/mL</td>
<td>35</td>
</tr>
<tr>
<td>Nitroglycerin, 5 mg/mL</td>
<td>30</td>
</tr>
<tr>
<td>Esmolol, 250 mg/mL</td>
<td>25</td>
</tr>
</tbody>
</table>

A previously healthy 40-year-old man was referred from another hospital where he was initially admitted for a 4-day history of nausea, general weakness, abdominal pain, diarrhea, and progressive oligo-anuria. The patient was oriented and had no neurological deficit.


L-Lactic Acidosis

- Type A
  - Shock
  - Acute Severe Hypoxia
  - Acute Severe Anemia

- Type B
  - Cyanide
  - Metformin
  - Malignancy
  - Thiamine Deficiency
  - NRTI (nucleoside reverse transcriptase inhibitors)
**Lactic Acidosis**

Linezolid inhibits bacterial protein synthesis via its action on bacterial ribosomal RNA.

The drug probably also impairs mammalian mitochondrial ribosomal RNA generation and thereby produces mitochondrial dysfunction.

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**Propofol - The Good**

- **Onset of action and recovery from its effects are very rapid.**
- Patients do not feel “groggy” after propofol use and indeed may awake feeling refreshed and with a sense of euphoria.
- **Has neuroprotective effects including inactivation of GABA receptors & blockade of excitatory neurotransmitters.** It reduces cerebral oxygen consumption and intracranial pressure. Also has antioxidant, anti-inflammatory & bronchodilator properties.

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**Propofol Infusion Syndrome (PRIS)**

- Anion Gap Metabolic Acidosis (L-Lactic)
- Acute Kidney Failure
- Rhabdomyolysis
- Heart Failure
- Hyperlipemia
- Brugada Syndrome

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A 22-yr man with a history of short bowel syndrome (due to a gunshot wound 5 years before) presents to the ED complaining of confusion and weakness. He takes no medications.

P Ex: Thin man, not malnourished. BP 110/80 mmHg, resp. 15/minute, Heart rate 82/minute. Afebrile. Has large abdominal surgical scar. Confused but no focal signs. Lab results: Na 134 mEq/L; K 5.0 mEq/L; Cl 92 mEq/L; HCO3 13 mEq/L. BUN, 5 mg/dl; Cr 0.4 mg/dl; Glu 110 mg/dl. ABG: pH 7.29; PO2, 133 mmHg; PCO2 29 mmHg; and HCO3 14 mEq/L. Lactate: 2 mmol/L; -OH butyrate 1 mmol/L. ETOH, methanol, and ethylene glycol all negative.

Which ONE of the following should be done to treat his metabolic acidosis?

A. Oral antibiotic therapy  
B. Intravenous infusion of Ringer’s lactate  
C. Acute hemodialysis  
D. Administration of fomepizole

LACTIC ACID: A Chiral Molecule  
Optical Isomers Exist

PYRUVATE

NADH  
NAD

L-LACTATE

d - LACTIC ACID  
Optical Isomers (Chiral Molecules)

Pathophysiology

- Altered Bowel Bacterial Flora - Gram-Positive Anaerobes especially Lactobacilli
- Increased Delivery of Carbohydrate to Gut Bacteria

Patients with Short Bowel Syndrome, Small Bowel Bypass, Bacterial Overgrowth - Especially After Increased Carbohydrate Loads &/or After Treatment with Antibiotics
Neurologic Signs & Symptoms
Prevalence in 29 Patients with d-Lactic Acidosis

- Altered Mental Status 100%
- Dysarthric Speech 65%
- Ataxia 45%
- Gait Disorder 35%

Weakness, Incoordination, Hostility, Nystagmus, Hostility, Hallucination, Paranoid, Headache

From Uribarri, Oh Carroll Medicine 1998

Antibiotics including metronidazole, neomycin, and vancomycin have been effectively used to decrease the density of D-lactate producing organisms.

Low carbohydrate diet (and/or the use of starch polymers rather than simple sugars) diminish carbohydrate delivery to the colon and may be helpful.

However, antibiotics can occasionally precipitate D-lactic acidosis in susceptible subjects by causing the overgrowth of Lactobacilli.

A 46-yo W woman admitted to BUMC with 5 days of N&V and development of metabolic acidosis and dyspnea

1 yr. Hx of similar recurrent episodes about q month. Hospitalized several times. The metabolic acidosis & Sx usually resolve with IV fluids

Long Hx frequent migraine headaches Rx – acetaminophen/Propoxyphene prn
Other Meds: Enalapril 10 mg/d & Premarin 0.625 mg/d

PE – Chronically ill appearing thin woman
BP 110/70 R22 P 120

HEENT – Unremarkable
Lungs – Clear
Heart – Tachycardia, No M
Abdomen – Mild diffuse tenderness
Ext – No Edema or Tenderness
Neuro – Alert, Oriented, No focal deficit

WBC: 20,000 – 15% bands and 78% polys
Hb 10.1 g/dl, Hct 32.2%
ESR 3

BUN 30; Cr 2.0 Glucose 534
GGT 1100 U/L; AST 2200 U/L; ALT 900 U/L,
LDH 2000 U/L; CK 159 U/L.

Plasma NH₄ 48
Alcohol level was undetectable.
Lumbar puncture was unremarkable.
Urine, blood, and CSF cultures all were negative.

Acetaminophen level 6.8 µg/ml (Therapeutic)
Plasma 5-oxoproline (GC-MS) was 6.4 mmol/L