Hyperkalemia: Pathophysiology and Therapy

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Basic Pathophysiology

• I. Potassium Homeostasis
  – Internal Balance
  – Electrochemical Gradient
  – Renal Excretion
    • Distal Tubule
  – Renin-Angiotensin-Aldosterone Axis

• II. Hyperkalemia
**K⁺ Homeostasis**

Total Body $K⁺ = 50-55$ mEq/Kg Wt

Net Absorption

100 mEq/d

- Extracellular Fluid
  - Potassium
  - 70 mEq
  - (3.5-5.5 mEq/L)

- Intracellular Fluid
  - 3500 mEq
  - (140-150 mEq/L)
  - Muscle 2700 mEq
  - Liver 250 mEq
  - Erythrocytes 250 mEq
  - Bone 300 mEq

- Renal excretion
  - 90 mEq/d

- GI excretion
  - 10 mEq/d
Internal Homeostasis of $K^+$

$Na^+ \quad Na^+ \quad Ca^{++} \quad Ca^{++} \quad Na^+$

$K^+$

$140 \text{ mEq/l}$

$PD = -90$

$K^+ = 4 \text{ mEq/l}$

$Na^+$

$Ca^{II}$

$H^+$

$ATP$
Potassium Cell Shifts: Major Transporters

**Drives K⁺ Into Cells**

- Insulin*
- β₂ Adrenergic Agonists*
- Alkalosis
- α Adrenergic Antagonists
- Anabolism
- Aldosterone?

**Drives K⁺ Out Of Cells**

- Mineral Metabolic Acidosis
- Hypertonicity (Hyperglycemia)
- β₂ Adrenergic Antagonists
- α Adrenergic Agonists
- Glucagon

Normal Electrochemical Gradient

\[
\frac{K_i}{K_o} = \frac{130}{4.0} = 32.5
\]

Nernst Equation

\[
PD = 58 \times \log \left( \frac{K_o}{K_i} \right) = -88
\]

\[K^+ = \sim 130\text{mEq/l}\]

\[K^+ = \sim 4.0\text{ mEq/l}\]
Cl⁻ → apical → Na⁺, K⁺ (Principal Cell)

Na⁺, K⁺ → ATP → basolateral → Na⁺, K⁺ (Principal Cell)

ECF Blood

3 Na⁺ → ATP → 2 K⁺ → 3 Na⁺ (Intercalated Cell (A))

H⁺, K⁺ → ATP → HCO₃⁻

Cl⁻ → Cl⁻
Factors Affecting Distal Tubule

Na$^+$ Reabsorption & The Secretion of K$^+$ & H$^+$

1. NaCl & NaAnion delivery
2. Volume
3. Aldosterone Level
4. Permeability of the luminal anions
5. K Status
6. Acid/Base Status
The Normal Renin-Aldosterone Feedback Loop

↓ EAB Volume → Renin → Angiotensin → Aldosterone

1. Decreased Renal Artery Pressure
2. JG Cells
3. Renin
4. Angiotensin I
5. Angiotensin II
6a. Pressor Effects
6b. Aldosterone Secretion
7. Sodium Retention
8. Increased EABV

Note: small increases in serum potassium also increase renin levels
HYPERKALEMIA
Hyperkalemia: Epidemiology

- Present in 1-10% of hospitalized patients (depends upon definition)
- The incidence of hyperkalemia with RAAS inhibitors in monotherapy is low (< 2%) in patients without predisposing factors.
- Increased with dual RAASi – up to 5%
- Increased with CKD, diabetes, heart failure- 5 to 10%

Hyperkalemia: RAASi

- Fogari et al: Lisinopril 20 mg for hypertension: 0.2 mg/dL rise in potassium
- Other studies: ACEi monotherapy: potassium levels > 5.5 mg/dL was 2% and levels > 6.0 mg/dL are rare
- “in the absence of renal insufficiency, azotemia, or heart failure, hyperkalemia is unusual”

Hyperkalemia: RAASi

- ARB monotherapy: associated with very small increases in potassium (0.1 mg/dL)
- Aldosterone antagonists: small increases in serum potassium (0.2 mg/dL)
- Direct renin inhibitors: hyperkalemia incidence similar to ACE inhibitors

Hyperkalemia: Associated Conditions

- 1. Heart Failure: increased rate compared to those w/o heart failure but remains low (about 2% with levels > 6.0 mg/dL)
- 2. Chronic Kidney Disease: observed increases in potassium are low (0.3 mg/dL) but severe CKD is generally not studied where the risk of hyperkalemia may be substantial
- In most cases, serious morbidity or mortality with these rises in potassium have not been seen
- Caveat: clinical studies may not be indicative of actual practice

**Differential Dx of Hyperkalemia**

- R/O Pseudohyperkalemia
  - In Test Tube
    - Warm Temperature
    - Fragility
    - Clotting (Serum vs Plasma)
    - Heparin (Reverse Pseudohyperkalemia)
  - In the Arm – Fist Clenching/Tourniquet

- K shifts out of Cells
- Impaired renal excretion
  - Always contributes to sustained hyperkalemia
- Excess $K^+$ intake may contribute
Pseudohyperkalemia

Familial Pseudohyperkalemia

Autosomal dominant trait
Enhanced temperature dependent $K^+$ leakage out of RBC’s
Maps to same gene locus as hereditary xerocytosis
(dessicocytosis, some forms of stomatocytosis)
Hyperkalemia

Excess intake
(usually in setting of impaired renal excretion)

- Recent ingestion of large amounts of orange/tomato/coconut /noni juice (Morinda citrifolia)
- Some pica syndromes
- Salt substitute
Other Drugs/Supplements and Hyperkalemia

• 1. Impair renal potassium secretion:
  – Amiloride, pentamidine, triamterene, trimethoprim
• 2. Decrease adrenal gland steroids:
  – Azole antifungals
• 3. Suppress renin release:
  – NSAIDS, cyclosporine, tacrolimus
• 4. Decrease aldosterone synthesis/action:
  – Aliskrein, ACE inhibitors, ARBs, heparins, mineralocorticoid receptor antagonists, yasmin
Other Drugs/Supplements and Hyperkalemia

5. Inhibit Na/K-ATPase:
   - Beta-blockers, digoxin and digoxin-like products (lilly of the valley, milkweed)

6. Increased Potassium Intake:
   - Penicillin G salts
   - Herbal Potassium Salts: alfalfa, dandelion, noni juice, hawthorn berries

7. Potassium Shifts in the Extracellular Space:
   - Amino acids (lysine, arginine), aminocaproic acid, hypertonic glucose, contrast media, succinyl chloride
Hyperkalemia

Cell Shift

- Cell injury: rhabdomyolysis, tumor lysis, massive hemolysis, ischemia
- Toxins/drugs: digoxin (Chan su), tetrodotoxin (Puffer Fish), succinylcholine
- Diabetic ketoacidosis, nonketotic hyperosmolar state
- Hyperkalemic periodic paralysis
CONSEQUENCES OF HYPERKALEMIA
Normal

Nernst Equation \[ PD = 58 \times \log \left( \frac{K_o}{K_i} \right) = -90 \]

\[ \frac{K_i}{K_o} = \frac{130}{4.0} = 32.5 \]

\[ K^+ = \sim 130 \text{ mEq/l} \]

\[ K^+ = \sim 4.0 \text{ mEq/l} \]
Hyperkalemia
Depolarization

Nernst Equation

$$PD = 58 \times \log \left( \frac{K_o}{K_i} \right) = -78$$

$$\frac{K_i}{K_o} = \frac{130}{7.0} = 18.6$$

$$K^+ = \sim 130 \text{ mEq/l}$$

$$K^+ = \sim 7.0 \text{ mEq/l}$$
EKG MANIFESTATIONS OF HYPERKALEMIA

- Peaked T wave
- Flattened P wave
- Prolonged PR
- Prolonged QRS
Sinus tachycardia with 1st degree A–V block
Right bundle branch block
Abnormal ECG

Technician: JAKE MARROQUIN

Referred by: ESHA

K=6.8
08-OCT-2009 17:53:46

BAYLOR HEALTH CARE SYSTEM

Vent rate 130 BPM
PR interval 10 ms
QRS duration 102 ms
QT/QTc 298/438 ms
P-R-T axes ± 0 -87

3
Undetermined rhythm
Low voltage QRS
Septal infarct (cited on or before Lateral infarct, possibly acute
Marked ST abnormality, possible inferior subendocardial injury
Marked ST abnormality, possible anterior subendocardial injury

Acute MI

Abnormal ECG
When compared with ECG of 09-SEP-2009 16:29,
Significant changes have occurred

Referral by: ESHA
Demographics completed by: HEATHER HENDERSON

Technician: NOLES
Test id:

COMMENTS:

I aVR V1 V4

II aVL V2 V5

III aVF V3 V6

25mm/s 10mm/mV 100Hz 7.1.1 12SL 237 CID: 1

SID: 01109011017 EID: 8008 EDT: 11:57 09-OCT-2009 ORDER: J322

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THERAPEUTIC ISSUES IN THE TREATMENT OF HYPERKALEMIA
Evidence Base

• Very few RCTs that guide therapeutic decisions.
• Most trials focus on Pk and not outcome measures such as mortality
• Recommendations are largely based upon opinions, consensus and can vary considerably between institutions
THERAPY OF HYPERKALEMIA #1

Direct Electrical Antagonism

- 10% Calcium Gluconate 10 mL IV
  (4.5 mEq of calcium) or

- 10% Calcium Chloride 10 ml IV
  (13.6 mEq of Calcium)
HYPERKALEMIA & THE RESTING POTENTIAL
EFFECT OF CALCIUM INFUSION ON MUSCLE THRESHOLD POTENTIAL

normal

depolarized

mVolts

0

Ca↑ TP

TP

RP

Normal

Hyperkalemia
THERAPY OF HYPERKALEMIA

#2

Shift K⁺ into Cells

- Regular insulin 10 U IV +
  50 mL of 50 % glucose then D 10% at about 75 ml/hr Glucose
  No glucose if baseline hyperglycemia exists
- Albuterol 10-20 mg in 4 mL of saline via IPPB (Usual “asthma” dose is 2.5 mg)
- NaHCO₃ 50-100 mEq IV
Rx of Hyperkalemia
Shifting $K^+$ into Cells

$K^+ = \sim 130$ mEq/l

Insulin
$\beta_2$ Agonists

$3 Na^+$
$2 K^+$

$3 Na^+$
$2 K^+$

ATP

$H^+$

Insulin

$HCO_3^-$
CHANGE IN PLASMA [K] WITH Rx
Hemodialysis Patients

Δ K
mEq/l

0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4

15 30 45 60
minutes

NaHCO₃
Insulin & Glucose
Albuterol
Albuterol, Insulin & Glucose

Allon et al KI 1990 & Blumberg et al KI 1992
EFFECT OF IV NaHCO₃ ON PLASMA [K]
Hemodialysis Patients

Blumberg et al KI 1992
THERAPY OF HYPERKALEMIA

#3 Remove from Body

• Improve Kidney Function – Volume Expansion When Indicated
• Loop &/or Thiazide Diuretics
• Induce Diarrhea
• Na-polystyrene sulfonate (Kayexalate®) 15-30 gm PO ? Sorbitol
• ?Kayexalate® Enema ?? Sorbitol
• Newer therapies: ZS-9, patiromer
Colonic Excretion

• Since renal excretion is the major route of potassium elimination, hyperkalemia is common in CKD patients
• Under these circumstances, potassium secretion in the distal colon is greatly increased
• Reflects increase in apical potassium permeability secondary to up-regulation of high conductance calcium-sensitive potassium channels (KCNMA1)

Sandle and Hunter 2010
THERAPY OF HYPERKALEMIA #4

Stop K Salts and K+ retaining Medications

• Salt Substitutes
• Parenteral or Oral K salts
• ACE Inhibitors/AR Blockers/Renin Inhibitors
• Spironolactone/Triamterene/Amiloride
• Trimethoprim
• β-Blockers
• Heparin
Metabolic Acidosis & K Shifts

- Inorganic (mineral acids) cause K⁺ shift not organic acids
- Diabetic ketoacidosis & ↑ K
  - Insulin deficiency
  - Hyperosmolality
- Lactic acidosis & ↑ K
  - Cell ischemia
  - Reduced GFR
- Epsilon-aminocaproic acid, a synthetic amino acid structurally similar to lysine and arginine does cause K shift out of cells
Impaired Renal K⁺ Excretion

• Primary decrease in mineralocorticoid activity
• Primary decrease in distal Na⁺ delivery
• Abnormal cortical collecting duct
  – Various forms of pseudohypoaldosteronism
Angiotensin –> Angiotensin II

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS**

**IMPAIRED RELEASE OF RENIN**

- NSAID’s
- Beta Blockers
- Cyclosporine, Tacrolimus
- Diabetes
- Elderly

**ANGIOTENSIN RECEPTOR BLOCKERS**

- Adrenal Gland

**IMPAIRED ALDOSTERONE METABOLISM**

**SODIUM CHANNEL BLOCKERS**

- Amiloride
- Triamterene
- Trimethoprim
- Pentamidine

**Adrenal Disease**

- Heparin
- Ketoconazole

**ALDOSTERONE RECEPTOR BLOCKERS**

- Spironolactone
- Eplerenone
- Yaz

Drospirenone
A Progestin with Mineralocorticoid Antagonist Activity

• The progestin component of some relatively new oral contraceptives – Yaz, Yasmin, Yasminelle

• The dose in OCPs has an effect like 25 mg spironolactone

• It may reduce BP

• It may generate hyperkalemia when other problems exist – ie CRD, use of other drugs which reduce K excretion, etc.
Chronic Management of Hyperkalemia

- D/C meds that interfere with K excretion
- Low K diet (<70 mEq/d)
- Assess volume and blood pressure
  - ↓ volume, Normal BP: consider fludrocortisone
  - ↑ volume, ↑ BP: consider
    - Diuretics
    - NaHCO₃
  - +/- Kayexalate (?) or newer resins