Diuretic Resistance
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Diuretic Resistance: When What You are Doing Stops Working

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Disclosures

• None, just working for The Man like all of us
A disease is not a disease unless it affects the kidneys

Joel Chinitz M.D. Philadelphia
A good heart and set of kidneys can withstand all but the most woefully incompetent fluid regime

Objectives

• Understand where in the kidney each class of diuretics work
• Discuss how the body responds to chronic diuretic therapy
• Discuss the causes of diuretic resistance
• Discuss strategies to overcome diuretic resistance
## Resting Fluid Balance

<table>
<thead>
<tr>
<th>Minimal obligatory water intake</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingested</td>
<td>500 ml</td>
</tr>
<tr>
<td>Water in food</td>
<td>600 ml</td>
</tr>
<tr>
<td>Water from oxidation</td>
<td><strong>500 ml</strong></td>
</tr>
<tr>
<td>Total</td>
<td><strong>1600 ml/day</strong></td>
</tr>
</tbody>
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<tr>
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<tbody>
<tr>
<td>Urine</td>
<td>500 ml</td>
</tr>
<tr>
<td>Skin</td>
<td>500 ml</td>
</tr>
<tr>
<td>Respiratory</td>
<td>400 ml</td>
</tr>
<tr>
<td>Stool</td>
<td><strong>200 ml</strong></td>
</tr>
<tr>
<td>Total</td>
<td><strong>1600 ml/day</strong></td>
</tr>
</tbody>
</table>
Sodium and Water in the Kidney

- 99% of filtered sodium is reabsorbed
- 1% excreted
- 99-99.5% of filtered water is reabsorbed
- 0.5-1% excreted
- In states of excess sodium and water—more excretion
- In dehydration—body holds onto sodium and water
Diuretics Definition

• A substance that will increase the output of urine
Sites of Action on the Nephron

- **Proximal Tubule**: Carbonic anhydrase inhibitors and Sodium Glucose Luminal Cotransporter inhibitors (SGLT-2)
- **Thick Ascending Limb**: Loop diuretics
- **Distal Tubule**: Thiazides
- **Distal Tubule/Collecting Duct**: Potassium sparing, mineralocorticoid receptor blockers
- **Multi-segmental**: Osmotic diuretics
Diuretic Actions on the Nephron

Why all these colors?
- Segment name in violet
- Diuretic name in pink
- Reabsorption in red
- Secretion in green
- Percentage in blue
- Hormone in orange

Loop of Henle

Loop diuretics

Acetazolamide
- Creatinine, Antibiotics, Diuretics, Uric acid

Proximal part
- Thiazides

Chlorothiazide and others

DCT

Distal part
- Osmotic, Ketanamid

Spironolactone

Amiloride, Triamterene

Furosemide, Bumetanide, Torsemide, Ethacrynic Acid

"PTH"

"Aldosterone"

"ADH"

Why not all these colors?
- Mannitol
- Osmotic

Cortex

Medulla

PCT

Osmotic

Mannitol

NaCl 67-40

H2O 85

HCO3-

Glucose, AA

NaCl 25

K 25

H2O

Desc. limb

Mag

Ca

Asc. limb

Mag

Ca
SGLT-2 Inhibitors

• Although not classified as a diuretic per se, they decrease reabsorption of sodium along with glucose in the proximal tubule leading to loss of sodium and water along with glucose in the urine.

• By blocking SGLT-1/2 the Sodium and Glucose is passed downstream
MOA of SGLT-2’s
Diuretic Effects of SGLT-2’s

• Decreased sodium reabsorption and osmotic diuretic effects
• 1.5-6kg weight loss, partially due to sodium and water loss
• ~4.45 mm Hg SBP decrease in SGLT-2 treated patients

*Diabetes Care* 2015;38: 2344-2353.
Carbonic Anhydrase Inhibitors

• *Weak diuretic* action leads to loss of Na, Cl and Bicarbonate in the urine leading to metabolic acidosis (induces a Proximal Type 2 RTA)

• Volume loss leads to *hypokalemia*

• *Indications*: glaucoma, altitude sickness (additive to respiratory alkalosis), idiopathic intracranial hypertension, epilepsy (topiramate), chronic metabolic alkalosis

• Acetazolamide (Diamox)

• Maybe considered as last resort add-on diuretic therapy
Carbonic Anhydrase Inhibitors

Carbonic anhydrase catalyzes the production of carbonic acid ($H_2CO_3$)

Carbonic anhydrase inhibitors (e.g. acetazolamide) inhibit carbonic anhydrase and promote $HCO_3^-$ loss

Reference [5]
Loop Diuretics

• Powerful medications used to mobilize fluid in CHF, cirrhosis, hypertension, CKD and nephrotic syndrome
• “High ceiling”-significant increased urine output up to a point
• Loop diuretics need to be bound to albumin and secreted in the proximal tubule. It then competes with Chloride, thus blocking the Na/K/2CL Symporter/Cotransporter (NKCCT-2) in the Thick Ascending Limb (TAL)
MOA Loop Diuretics

Mechanism of Action of Loop Diuretic

Thick ascending loop of Henle
Tubular lumen
Loop Diuretics

- *The Na/K/2Cl* (NKCCT-2) symporter is responsible for 20-40% of the reabsorption of Na, K and Cl.
- By blocking the NKCCT-2 sodium is sent downstream and excreted
- Euvolemic patients will have a urine Na content of ~75 mEq/l=1/2 NS
- Also leads to loss of Magnesium and Calcium
Loop diuretics

• Furosemide, torsemide, bumetanide, ethacrynic acid (only agent that can be used in a patient with a true sulfa allergy)

• **Variable** oral **absorption** from the **GI tract** can influence diuretic actions, torsemide has an advantage of **consistent** GI uptake

• In **advanced CHF or CKD** doses need to be **increased** for therapeutic effect and frequency e.g. Q8-12 hours

• **Chronic** therapy will lead to **decreased effect** due to hypertrophy of Na receptors distally/downstream

• Increase calcium loss in the urine in hypercalcuria
Thiazide and Thiazide-like Diuretics

- Medications that **inhibit** the actions of the **Sodium Chloride Cotransporter/Symporter** (NCCT) in the early segment of the Distal Convoluted Tubule, sending Sodium downstream
- Responsible of about 3-5% of Na reabsorption
- **Long term** effects hypotensive effects may be due to arteriolar vasodilation
- When combined with loop diuretic can diminish diuretic resistance
- However, thiazides can lead to greater degree of hyponatremia as compared to loop diuretics
Mechanism of Action of Thiazide
Thiazides

- Enhanced Calcium **reabsorption** can prevent renal lithiasis
- Thiazides **augment** the effect of most classes of antihypertensives
- Clinically Chlorthalidone and Indapamide are **more** effective than HCTZ in part due to longer $T_{1/2}$
- **Use**: HTN-1\textsuperscript{st} or 2\textsuperscript{nd} line medication, CHF, edematous states, prevention of calcium stones
- Effective to a GFR of 30 ml/min
- Metolazone is no more effective than Chlorthalidone
Potassium Sparing Diuretics

• **Block Epithelial Sodium Channel** (ENaC) in the Principal cells of the Collecting Duct, thus **no Sodium reabsorbed** into the cell **or Potassium is secreted** into the lumen, thus Sodium is passed downstream

• Responsible for ~3% of Sodium reabsorption

• Mild metabolic acidosis and hyperkalemia, mimics a Distal Type 4 RTA

• Can be used in combination with other classes in diuretic resistance
Potassium Sparing Diuretics

Potassium Sparing Diuretics

Lumen-urine

Collecting tubule

Interstitium-blood

Principal cell

ENaC

Na+

K+

Aldosterone

ATP

Na+

K+

Intercalated cell

ATP

HCO₃⁻

Cl⁻
Potassium Sparing Diuretics

• Amiloride, triamterene, trimethoprim (part of Bactrim), may be combined with a thiazide
• Use: HTN, may prevent toxic effect of Lithium, CHF, edematous states
Mineralocorticoid Receptor Antagonists (MRAs)

• Block the effects of aldosterone and similar mineralocorticoids
• Act of the MCR in the Principal cells of the Collecting Duct and other sites, preventing Sodium reabsorption and passing it downstream
• Similar MOA as Potassium sparing diuretics
• Spironolactone and Eplerenone
• **Used** in HTN, CHF, CKD, Cirrhosis
• Hyperkalemia and metabolic acidosis as with K sparing diuretics
• **Improved** survival in CHF, even w/ worsening CKD

MRAs MOA
Vasopressin Receptor Antagonists (VRA)

- **Block** the actions of Antidiuretic Hormone at the $V_1$ and/or $V_2$ receptors leading to a free water diuresis (induces a nephrogenic diabetes insipidus)
- Tolvaptan $V_2$ Concerns about liver and renal effects
- Conivaptan $V_{1a}$ and $V_2$
- **EVEREST Trial**-Tolvaptan in ADCHF- *no* long term benefit vs placebo, though some short term fluid/symptom improvement was noted in treatment arm

_Eur Heart J_ 2009;30:2233-2240
How VRAs Work

- Concentrated urine
- Decreased free water clearance
- Lowering of serum sodium

- Dilute urine
- Increased free water clearance
- Raising of serum sodium
Vasopressin Receptor Antagonists

- **Use**: SIADH, Cirrhosis/ESLD, CHF, polycystic kidney disease
- **BUT**—may lead to overcorrection of hyponatremia and CNS damage (FDA black box warning)
- Not sure where this class of medications will fit in clinically
Diuretic Resistance

- **Definition**: the inability to mobilize and excrete excessive extracellular fluid, usually due to under dosage or failure of current diuretic regime.
Causes of Diuretic Resistance

• Increased sodium reabsorption at other sites in the kidney downstream (remodeling)
• Under dosage and frequency
• Excess salt intake
• Hypoalbuminemia
• Decreased gut absorption
• Decreased diuretic secretion in urine
• Decompensated heart function and/or renal function
• NSAIDs and other medications
How the Body Responds to Volume Depletion and CHF

Hypoperfusion & LOW CO/BP (Volume depletion, shock, sepsis, CHF)

↑ SNS (Epi N.E.) → V.C. / Ventricular Contraction

⇒ RAAS (AT II/Aldo) V.C., Na/H₂O ᵃ

⇒ ↑ ADH V.C. H₂O / Na ᵃ

⇒ ↑ C.O. / BP

⇒ ↑ Atrial Naturetic Peptide (ANP)

 Suppresses: SNS, RAAS, ADH

Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
</tr>
<tr>
<td>Epi</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>N.E.</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>V.C.</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>✱</td>
<td>Reabsorption</td>
</tr>
<tr>
<td>RAAS</td>
<td>(Renin Angiotensin Aldosterone System)</td>
</tr>
<tr>
<td>ADH</td>
<td>Antidiuretic Hormone</td>
</tr>
<tr>
<td>ANP</td>
<td>Atrial Naturetic Peptide</td>
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How the Kidney Adapts to Chronic Diuretic Therapy-Nephron Remodeling

- Sodium uptake from the tubule of blocked by a diuretic
- More sodium is delivered distally, and there is an increase in the number of sodium coupled exchangers to reabsorb the excess sodium in the tubule
- The body never wants to lose sodium or water-no matter how badly it needs to

NEJM 2018; 378:684-685
Underdosage

• **Threshold rate**: Dose of diuretic must overcome the reabsorption at other sites. In chronic diuretic therapy, especially with loops, there is hypertrophy of the distal cells (Na/Cl symporter and ENaC) to increase sodium reabsorption eventually negating the original dose.

• **Diuretic Braking**: Diminished diuretic effect with subsequent dosages

• **Maximum effective dose**: dose at which loop Na/Cl transport will be completely inhibited
Once Daily Diuretic Dosage-No Net Fluid Loss

• Initial diuretic effect for several hours leads to enhanced sodium and water reabsorption with no net fluid loss
Refill in Diuretic Therapy

Concept of Plasma Refill Rate in ADHF

Diuretics to increase sodium loss and decrease venous pressures

Plasma Volume Loss
100 – 300 mL/hr

Diuresis

4 L

Plasma Refill Rate
<100 mL/hr

0 L
Excess

Extra cellular Volume
Underdosage

Rule of thumb:
• Increase dose-IV 2x oral dose minimum
  AND
Increase frequency Q 8, or 12 hours
• Increase dose in CKD-don’t send a baby in to do a grown-up’s job!
• 20mg of Lasix with a creatinine of 3.2 mg/dl will have little effect
Excess Salt Intake

Recent data has challenged severe salt restriction, no randomized trials have looked at this in CHF

- Will negate the effects of diuretics and most antihypertensive agents
- Think SALT not just sodium, 3-4 gm/da (???)
- If 24 hour urine sodium >100 mEq/l=non compliance
- In a review of 32 studies a “J-shaped curve” of increased CV Risk in daily Na intake <2.5 gm/day and > 6.0 gm/day

*Curr Hypertens Rep. 2012;14:193-201*
NSAID/Cox-2 Inhibitor Use

• NSAIDs and COX-2 inhibit prostaglandins that vasodilate the afferent arteriole, resulting in vasoconstriction and decreased glomerular perfusion

• Certain prostaglandins have naturetic actions, inhibited by these meds

• Can cause AKI

• PPI’s, herbal medications i.e. licorice root mimics hyperaldosteronism
Hypoalbuminemia

- Albumin less than 2.2 g/dl leads to low oncotic pressure and extravasation of fluid into tissues.
- Generalized edema from CHF, cirrhosis, nephrotic syndrome, low oncotic pressure and malnutrition impair absorption of oral diuretics.
- Torsemide has more consistent gut absorption in CHF, thus better diuretic action.

*Future Cardiol* 2012; 169:707-728
Decreased Diuretic Secretion in the Kidney

- Hypoperfusion from hypotension or CHF
- Worsening renal function, NSAIDs compete with diuretics for secretion
- 95% protein bound (low albumin=less diuretic binding)
- Loop diuretics bind to albumin and are absorbed in the proximal tubule cell and then secreted as a free diuretic
- The free diuretic goes to the thick ascending limb where is competes with chloride at the Na/K/2 Cl pump
- Low oncotic pressure leads to diminished binding of albumin to the loop diuretic, thus limited uptake and action

Decreased Diuretic Secretion in the Kidney

• Increased dose needed in CKD or AKI
• Albumin supplementation when level is <2.2g/dl (?)
• Posture: supine _more_ diuretic effect, upright-increased NE and renin/aldosterone _less_ diuretic effect
• Continuous infusion vs bolus (maybe/maybe not-DOSE trial 2011)

Renal Insufficiency and Diuretic Resistance

Dose Response for Loop Diuretic in Renal Insufficiency

\[ \text{FENa (\%)} \]

\[ \text{Serum Conc (Log mass/vol)} \]

↓ Urinary delivery ⇒
Decompensated CHF/CKD/AKI

- Diminished perfusion of the kidney leads to perceived volume depletion and increased catecholamines, RAAS activity, and ADH with enhanced sodium and water reabsorption.
- **Treat/Tweak CHF:** ACE-I/ARB/MRA, adrenergic blockage (carvedilol), nitrates.
- Blood pressure control.
- Nutrition-salt restriction improved diet.
How the Body Responds to Volume Depletion and CHF

Hypoperfusion & \textit{LOW} CO/BP
(Volume depletion, shock, sepsis, CHF)

\begin{itemize}
\item \textbf{↑ SNS} (Epi N.E.)
\item \textbf{RAAS (AT II/Aldo)} V.C., Na/H_2O \textcircled{R}
\item \textbf{↑ ADH} V.C. H_2O / Na \textcircled{R}
\end{itemize}

\textbf{V.C. / Ventricular Contraction}

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\textbf{Suppresses: SNS, RAAS, ADH}

**Glossary**

- **SNS**: Sympathetic Nervous System
- **Epi**: Epinephrine
- **N.E.**: Norepinephrine
- **V.C.**: Vasoconstriction
- **R**: Reabsorption
- **RAAS**: (Renin Angiotensin Aldosterone System)
- **ADH**: Antidiuretic Hormone
- **ANP**: Atrial Naturetic Peptide
Diuretic Resistance in Decompensated CHF
Approach to a Diuretic Resistant Patient

• Are they taking the medication and as directed?
• **Salt intake**—just because it does not taste salty does not mean it is low sodium chloride
• **Other medications:** herbal meds-NSAIDs, PPI’s, COX-2 inhibitors, licorice root, herbal products-mimics hyperaldosteronism
• **Worsening:** renal, cardiac, liver function or any combination of
• Hypothyroidism (amiodarone?)
Approach to a Diuretic Resistant Patient (2)

- **Increase** the dose *and* frequency of the loop diuretic
- **Consider** oral *torsemide* over oral furosemide (better gut absorption, longer $T_{1/2}$)
- **Add** a thiazide (chlorthalidone, indapamide or metolazone)
- **Add** a mineralocorticoid receptor blocker or K-sparing agent (spironolactone, eplerenone, amiloride or triamterene)
- Address **other** treatments, adrenergic blockade, ACE-I or ARB, but not together
- **Compression** of LE’s with ACE wraps and SCDs
- **Paracentesis**: decreases intraabdominal pressure
Effects of Sequential Nephron Segment Blockade on Diuretic Resistance

- Improved creatinine
- Fluid mobilization/loss
- 3 segments blocked: TAL, NCCT, ENaC

Diuretic Actions on the Nephron

Renal physiology & diuretics

Acetazolamide
Creatinine, Antibiotics, Diuretics, Uric acid

PCT
Osmotic
Mannitol

Cortex
Medulla

NaCl 67-40
K H2O 85
HCO3-
Glucose, AA

Proximal part
Thiazides

Chlorothiazide
and others

NaCl 10
Ca

PTH
Aldosterone

DCT
K
H
Urea

NaCl 2-5
H2O

Furosemide,
Bumetanide,
Torsemide,
Ethacrynic Acid

Distal part
Osmotic, K-sparing

Amiloride,
Triamterene

Spironolactone

Collecting duct and tubules

Osmotic
Mannitol

Why all these colors?
Segment name in violet
Diuretic name in pink
Reabsorption in red
Secretion in green
Percentage in blue
Hormone in orange

Loop of Henle
Loop diuretics

Mg
Ca

Mg
Ca

NaCl 25
K
H2O

Desc. limb

Asc. limb

H2O

"ADH"
When Maximum Therapy Fails

• Isolated ultrafiltration/dialysis: iso-osmotic fluid removal
• Can correct underlying acidosis which can improve cardiac function
• Correction of anemia
• Don’t overlook salt intake!
Summary of Diuretic Resistance

Figure 3: Mechanisms of loop diuretic resistance
Remember

• The body *never* wants to lose salt or water, no matter how desperately it needs to

• Sequentially blocking sodium and water reabsorption with help to attenuate this normal physiological response - think breaking links of the chain
Thank you

Questions?

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