The Art and Science of Diuretic Use

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Diuretics effective for the treatment of edema have been available since the 16th century.

Mercurous chloride was known by Paracelsus to be diuretic.

In 1930, Swartz discovered that the antimicrobial sulfanilamide could be used to treat edema in patients with congestive heart failure due to an increase in renal Na⁺ excretion.

Most modern diuretics were developed when side effects of antibacterial drugs were noted, which included changes in urine composition and output.

Except for spironolactone, diuretics were developed empirically, without knowledge of specific transport pathways in the nephron.
Development of antihypertensive therapy

- **Direct vasodilators**
- **Alpha blockers**
- **Loop diuretics**
- **Non-DHP CCBs**
- **Beta blockers**
- **Central alpha₂ agonists**
- **ACE inhibitors**
- **ARBs**
- **Renin inhibitors**

**Effectiveness**

**Tolerability**

- **Thiazide diuretics**
- **DHP CCBs**
- **Aldosterone receptor antagonists**

**Periods:**
- **1940s**
- **1950**
- **1957**
- **1960s**
- **1970s**
- **1980s**
- **1990s**
- **2007+**

DHP, dihydropyridine; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker.
Hemodynamic and hormonal effects of thiazide diuretic therapy

### BP-Lowering Treatment Trials

**Comparisons of different active treatments**

<table>
<thead>
<tr>
<th>BP Difference (mm Hg)</th>
<th>Relative Risk</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE vs D/BB</td>
<td>2/0</td>
<td>1.09</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>0.93</td>
</tr>
<tr>
<td>ACE vs CA</td>
<td>1/1</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>Coronary Heart Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE vs D/BB</td>
<td>2/0</td>
<td>0.98</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>1.01</td>
</tr>
<tr>
<td>ACE vs CA</td>
<td>1/1</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE vs D/BB</td>
<td>2/0</td>
<td>1.07</td>
</tr>
<tr>
<td>CA vs D/BB</td>
<td>1/0</td>
<td>1.33</td>
</tr>
<tr>
<td>ACE vs CA</td>
<td>1/1</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*CA, calcium antagonist; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, Beta Blocker; D, Diuretic.*
<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Recommended Drugs</th>
<th>Clinical Trials Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>Diuretic</td>
<td>BB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Post MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High CHD Risk</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent Stroke Prevention</td>
<td></td>
<td>*</td>
</tr>
</tbody>
</table>

Aldo ANT: Aldosterone Antagonist; ACEI: angiotensin-converting enzyme inhibitor
Effect of Antihypertensive Treatments on Left Ventricular Mass Regression

Newer Antihypertensive Agents Significantly Reduce Left Ventricular Mass Index Compared to β-Blockers

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ LVMI at BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs</td>
<td>13%*</td>
</tr>
<tr>
<td>CCBs</td>
<td>11%*</td>
</tr>
<tr>
<td>ACEIs</td>
<td>10%*</td>
</tr>
<tr>
<td>Diuretics</td>
<td>8%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>6%</td>
</tr>
</tbody>
</table>

*P<.05 compared to β-blockers.
The Systolic Hypertension in the Elderly Program (SHEP) Trial Design

IC = initial contact; BV1 = baseline visit 1.

Randomized, double-blind, multicenter trial
33,357 subjects, aged ≥ 55 y, with stage 1 or stage 2 hypertension
and ≥ 1 CHD risk factor or clinical cardiovascular disease*

Primary outcome: Superiority of newer agents over Chlorthalidone for Fatal CHD or non-fatal MI

Secondary outcomes: All-cause mortality; Stroke;
Combined CHD†; Combined CVD‡

Mean follow-up: 4.9 years

CHD, coronary heart disease; MI, myocardial infarction; CVD, cardiovascular disease.

* Previous (>6 mos) MI or stroke, LVH, type 2 diabetes, current smoker, HDL-C <35 mg/dL, other documented CVD.
† Primary outcome, coronary revascularization, hospitalized angina.
‡ Combined CHD, stroke, treated angina, heart failure, peripheral vascular disease.

ALLHAT: Primary End Point*

*Primary end point = fatal CAD or nonfatal MI.

43.2% lower onset of new diabetes with lisinopril compared to chlorthalidone ($P \leq 0.001$ at 4 years)

Class Effect
Diuretics

- There are obvious differences, which separate thiazide and loop diuretics.
- Amongst thiazide-type diuretics there is clearly a hierarchy for effect – less-based on potency than on duration of action. It is unclear how this relates to outcomes and/or level of blood pressure control until these issues are better studied.
- Outcomes-based trials succeeding with one thiazide-type diuretic should have that compound advocated for similarly-styled patients.
Blood Pressure Changes
Hydrochlorothiazide vs chlorthalidone

Rationale for Combination of an ACE inhibitor of an ARB With a Diuretic

Diuretic Effects

Volume Depletion → JG Cells → Renin Release → Renin → Angiotensin I → Angiotensin II → AT₁ Receptor → Vasoconstriction

Less Na⁺ Reabsorbed → Distal Tubule → Na⁺ Diuresis

ARB
"I’m going to give you something that works like a diuretic, but costs much, much more."
Arterial Underfilling in Patients with HF: Causes, Consequences and Counter-regulatory Mechanisms

↓ Cardiac output

↓ Arterial underfilling

↑ Peripheral vascular resistance

↓ Peripheral vascular resistance

↑ Renal sodium and water retention

↓ Restoration of arterial circulatory integrity

↑ Cardiac output

Activation of Neurohormonal Vasoconstrictor Systems and Renal Sodium and Water Retention

High-output cardiac failure:
- ↓ Peripheral vascular resistance
- ↑ Nonosmotic vasopressin release

Low-output cardiac failure:
- ↓ Cardiac output
- ↑ Renin Angiotensin Aldosterone activity

↓ Fullness of the arterial circulation
↑ Sympathetic nervous system activity

Diminished renal hemodynamics and renal sodium and water excretion

Thiazides
Inhibit active exchange of Cl-Na in the cortical diluting segment of the ascending loop of Henle

K-sparing
Inhibit reabsorption of Na in the distal convoluted and collecting tubule

Loop diuretics
Inhibit exchange of Cl-Na-K in the thick segment of the ascending loop of Henle
Neurohormonal Actions Leading to Diuretic Resistance

**Proximal Tubule**
Angiotensin II increases sodium reabsorption

**Glomerulus**
Norepinephrine (and endothelin) decrease renal blood flow and GFR

**Collecting Duct**
Aldosterone increases sodium reabsorption

Pearls

- All diuretics are not equal
  - Chlorthalidone is highly recommended over loop diuretics –
  - Loop diuretics increase Ca excretion by 2-3X
  - Elderly women: decrease Ca loss and osteoporosis
  - CHF: prevent Ca loss – prevents increase release of parathyroid hormone – prevents heart disease
Pharmacokinetics and Pharmacodynamics in Diuretic Resistance

- Dose
- Bioavailability
- Tubular secretory capacity
- Role of absorption
- Time course of delivery

Maximal Response

Altered dose-response relationship
Braking phenomenon

Threshold

Braking Phenomenon

- The braking phenomenon (postdiuretic sodium retention) describes avid sodium retention that can develop in response to a rapid diuresis, thereby limiting response to further doses of diuretics.
- The braking phenomenon may occur during either short-term or long-term therapy and is due to hemodynamic and neurohumoral changes produced by rapid diuresis.
Reaccumulation of Sodium Despite Ongoing Furosemide Treatment

N = 6
Treatment = IV furosemide 40 mg qd +/- oral captopril (ACEI)25 mg q6h
Tubular Effects of Chronic Loop Diuretic Therapy

Distal Tubular Cell Hypertrophy

Control

Loop Diuretic

Ellison D et al. JCI 83:113, 1989
Pearl

• In addition to the braking phenomenon, diuretic tolerance may occur as a longer-term process where the continued exposure of the distal tubule to a high sodium load results in distal tubular cell hypertrophy and an excessive "recapture" of sodium delivered from more proximal locations.

• Distal tubular hypertrophy can be altered by combining a thiazide-type diuretic with a loop diuretic.
Relationship Between Serum Creatinine and Glomerular Filtration Rate (GFR)

Creatinine Clearance

\[
\frac{U_{cr} \cdot V}{P_{cr}}
\]

\(P_{cr}\)
Serum Creatinine (mg/dL)

Graph showing the relationship between serum creatinine and glomerular filtration rate (GFR). The graph includes a mathematical expression for creatinine clearance and a curve that illustrates the decline in GFR as serum creatinine increases.
Determinants of weight loss with diuretic therapy

- Level of sodium intake (2 Gm diet)
- Blood pressure at the time of diuretic dosing
  - Separate times of adm. of antihypertensives and diuretics
- Body position
  - Supine position increases BP and diuresis
- Time since last diuretic dose
- Absorption pattern of the diuretic
Higher Doses of Loop Diuretic Are Associated With Increased Mortality in Severe HF

- Retrospective analysis of 1153 pts with advance HF from PRAISE study
- Loop diuretic above and below median compared
- High diuretic use independent predictor of:
  - Total mortality (HR 1.37; P+.018)
  - SCD (HR 1.39; p=.42)
  - Metolazone use also independent predictor of mortality

Diuretic Use and the Risk of Mortality in Patients with Left Ventricular Dysfunction

Mortality Risk by Loop Diuretic Use at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Diuretic (n=2901)</th>
<th>No Diuretic (n=3896)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Incidence</td>
<td>N</td>
</tr>
<tr>
<td>Death: all cause</td>
<td>1013</td>
<td>12.8</td>
<td>586</td>
</tr>
<tr>
<td>CV Death</td>
<td>903</td>
<td>11.4</td>
<td>510</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>241</td>
<td>3.1</td>
<td>183</td>
</tr>
</tbody>
</table>

SOLVD database
Cooper HA et al. Circulation. 1999; 100(12): 1311
Reducing Use of IV Diuretics and Resistance in Heart Failure

- Restrict sodium intake
- Eliminate NSAIDs and COX-2 inhibitors\(^1\)
- Give continuous IV infusion rather than bolus \(^2,3\)
- Combine loop diuretic with thiazide diuretic\(^4\)
- Combine with nesiritide\(^5\) (B-type natriuretic peptide)
- Combine with vasopressin antagonist \(^6\)
- Preserve glomerular filtration rate\(^7\)

Potential Effects of NSAIDs on Renal Physiology

- Arachidonic acid
  - COX-1
  - COX-2
- PGE$_2$
  - Sodium retention
    - Peripheral edema
    - ↑ Blood pressure
    - ↑ Weight
    - CHF (rarely)
- PGI$_2$
  - Hyperkalemia
  - Acute renal failure

CHF = congestive heart failure.
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Plasma Renin Activity and Aldosterone before and after Diuretic Treatment

<table>
<thead>
<tr>
<th></th>
<th>Before Diuretic (n = 12)</th>
<th>After Diuretic (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma Renin Activity (ng/mL/h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma Aldosterone (pmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Changes in SVI and Left Ventricular Filling Pressure After Diuretic Treatment

N = 15
SVI=stroke volume index
Pharmacokinetics and Pharmacodynamics in Diuretic Resistance

Sodium Excretion Rate

- Dose
- Bioavailability
- Tubular secretory capacity
- Role of absorption
- Time course of delivery

Threshold

Maximal Response

Efficiency

- Altered dose-response relationship
- Braking phenomenon

Loop Diuretic Excretion Rate
Reducing Use of IV Diuretics and Resistance in Heart Failure

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- Combine with nesiritide
- Combine with vasopressin antagonist
- Preserve glomerular filtration rate

Principle of sequential nephron blockade
URINE Volume (ml/Day)

URINE Na (mEq/Day)

URINE K (mEq/Day)

DAYS

G.P.

FUROSEMIDE 320 mg

METOLAZONE 5020
## Eplerenone versus Spironolactone

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eplerenone</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sex Hormone Adverse Effects</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>- Gynecomastia / Mastodynia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Impotence/menstrual irregularities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in Serum Digoxin Level</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP 3A4 metabolism</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Renal failure/hyponatremia</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pharmacology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Long half-life</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>- Active metabolites</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Mechanisms of Drug-induced Hyperkalemia

Reducing Use of IV Diuretics and Resistance in Heart Failure

- Restrict sodium intake
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- Combine with nesiritide\(^5\)
- Combine with vasopressin antagonist \(^6\)
- Preserve glomerular filtration rate\(^7\)

Design

Three-arm, open-label, crossover
Each treatment day followed by one-day washout

Treatment A  Furosemide 40 mg IV bolus over 2 mins

Treatment B  Nesiritide 2 μg/kg IV bolus
then 0.01mcg/kg/min for 6 hrs

Treatment C  Furosemide 40 mg IV bolus over 2 mins
              + Nesiritide (started 15 mins before)
Urinary Sodium Excretion Rate

- **Baseline**
- 0 to 4
- 4 to 10
- 10 to 22

**Time Intervals (hrs)**

**Urinary Na (umo/min)**

- **Natrecor**
- **Furosemide**
- **Natrecor + Furosemide**
Urinary Flow Rate

Baseline 0 to 4 4 to 10 10 to 22

Time Intervals (hrs)

- Natrecor
- Furosemide
- Natrecor + Furosemide
Reducing Use of IV Diuretics and Resistance in Heart Failure

- Restrict sodium intake
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# AVP Receptor Antagonists in Clinical Trials

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Tolvaptan</th>
<th>Lixivaptan</th>
<th>SR-121463</th>
<th>Conivaptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral/IV</td>
<td>IV</td>
</tr>
<tr>
<td>Urine volume</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Na⁺ excretion/24 hours</td>
<td>⇔</td>
<td>⇔ low dose</td>
<td>↑ high dose</td>
<td>⇔</td>
</tr>
</tbody>
</table>

These drugs are under development and are not approved for use by the FDA.

<table>
<thead>
<tr>
<th>Neurohormones</th>
<th>Tolvaptan</th>
<th>Loop Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Norepinephrine</td>
<td>⇒ (?)</td>
<td>↑</td>
</tr>
<tr>
<td>- Plasma renin activity</td>
<td>⇒ (?)</td>
<td>↑</td>
</tr>
</tbody>
</table>

Vasopressin-receptor antagonists versus loop diuretics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tolvaptan</th>
<th>Loop Diuretics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Sodium</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Serum Potassium</td>
<td>⇒</td>
<td>↓</td>
</tr>
<tr>
<td>Plasma Osmolality</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>⇒</td>
<td>May precipitate</td>
</tr>
<tr>
<td>BUN/Creatinine</td>
<td>⇒</td>
<td>May ↑</td>
</tr>
<tr>
<td>Renal Blood Flow</td>
<td>⇒ (?)</td>
<td>↓</td>
</tr>
<tr>
<td>GFR</td>
<td>⇒ (?)</td>
<td>↓</td>
</tr>
<tr>
<td>Neurohormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Norepinephrine</td>
<td>⇒ (?)</td>
<td>↑</td>
</tr>
<tr>
<td>- Plasma renin activity</td>
<td>⇒ (?)</td>
<td>↑</td>
</tr>
</tbody>
</table>
Short-Term Effect of Tolvaptan on Renal Parameters

Burnett et al. Abstract presented at the AHA 2003; November 9-12, 2003; Orlando, Fla.
Vasopressin Antagonist for Heart Failure: ACTIV in CHF Trial

Mean Body Weight Changes during Hospitalization

**Kg**

<table>
<thead>
<tr>
<th></th>
<th>24 Hours</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td>Tolvaptan 30 mg</td>
<td>-4</td>
<td>-4</td>
</tr>
<tr>
<td>Tolvaptan 60 mg</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>Tolvaptan 90 mg</td>
<td>-2</td>
<td>-2</td>
</tr>
</tbody>
</table>

* p<0.05 vs Placebo

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- Restrict sodium intake
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- Preserve glomerular filtration rate\(^7\)

Role of Ang II in Glomerular Function in HF

- Increased Filtration
- Increased Glomerular Pressure
- Efferent Arteriolar Constriction
- Reduced ejection fraction
- Decrease in Afferent Arteriolar Blood Flow

Courtesy of Domenic Sica, M.D.
Role of Ang II in Glomerular Function in HF Treated

- Increased Filtration
- Reduced blood pressure
- Decrease in Afferent Arteriolar Blood Flow

Decreased Glomerular Pressure

Efferent Arteriolar Dilation

Blood Flow

Angiotensin II

Courtesy of Domenic Sica, M.D.