Pharmacology of Resistant Hypertension

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Objectives

• Describe the general approach to the drug management of resistant hypertension
• Recognize commonly prescribed medications that may impede blood pressure control
• Compare and contrast the pharmacokinetics/ancillary properties of antihypertensive agents to select the most appropriate agent when presented with a patient case
• Apply the concept of plasma renin activity to help guide treatment decisions with antihypertensive agents

Presenter Disclosure Information

Financial Disclosure: I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant money for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Other Disclosures: I have participated in the development of the “PRA and HTN” app for the iPhone and Android smartphones. The app guides the user in the use of plasma renin activity to guide anti-hypertensive therapy. I received no compensation for its development or for its use which is available for download free of charge.

The views expressed in this presentation reflect those of the author, and not necessarily those of the Department of Veterans Affairs.

Consequences of Uncontrolled Hypertension


Prevalence, Treatment, and Control of Hypertension

Resistant Hypertension

- Failure to achieve goal blood pressure in adherent patients despite 3 antihypertensive agents from different classes
  - Ideally one agent should be a diuretic
  - All should be at optimal doses
- Includes patients whose blood pressure is controlled but require 4 or more medications

Prevalence of Resistant Hypertension

- Observational estimates
  - NHANES 2005-2008 – 20.7%
  - Tertiary Hypertension Centers – 11-38%
  - ASH (Carolinas, Florida, Georgia Chapter) 2007 – 16.2%
- Clinical trial estimates
  - ALLHAT, ASCOT, ACCOMPLISH, LIFE, CONVINCE, and INVEST suggest up to 35%
  - Difficult to establish

Current Oral Antihypertensive Agents

- Bumetanide
- Ethacrynic acid
- Furosemide
- Lasix
- Hydrochlorothiazide
- Chlorothiazide
- Indapamide
- Chlorothalidone
- Meticlozine
- Amiloride
- Triamterene
- Spironolactone
- Propranolol
- Atenolol
- Acebutolol
- Metoprolol
- Nadolol
- Nebivolol
- Bisoprolol
- Pindolol
- Timolol
- Bucindolol
- Carvedilol
- Labetalol
- Captopril
- Enalapril
- Fosinopril
- Moexipril
- Quinapril
- Ramipril
- Trandolapril
- Benazepril
- Lisinopril
- Perindopril
- Azilsartan
- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan
- Doxazosin
- Terazosin
- Prazosin
- Amlodipine
- Felodipine
- Isradipine
- Nifedipine
- Nimodipine
- Nitrendipine
- Dilazem
- Verapamil
- Clonidine
- Guanabenz
- Guanfacine
- Methylidopa
- Minoxidil
- Hydralazine
- Guanethidine
- Reserpine

The question remains: What approaches can be used to improve control, particularly in patients with resistant hypertension?
**Patient Characteristics Associated with Resistant Hypertension**

- High baseline blood pressure
- Older age
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- African American race
- Female gender
- Residence in Southeastern United States

**Lifestyle Factors Contributing to Resistant Hypertension**

- Obesity or overweight
- High salt diet
- Physical inactivity
- Ingestion of low-fiber, high-fat diet
- Heavy alcohol ingestion

**General Approach to Resistant Hypertension**

- Confirm treatment resistance
- Exclude pseudoresistance (24hr measurements)
- Address contributing lifestyle factors
- Discontinue or minimize interfering substances
- Screen for secondary causes of hypertension
- Document target organ damage
- Confirm appropriate treatment

**Primary Cause of Resistant Hypertension**

- Drug-related causes 58%
- Nonadherence 15%
- Psychological causes 9%
- Secondary HTN 5%
- Interfering substances 1%
- Office resistance 6%
- Unknown 6%

**Substances Impeding Blood Pressure Control: Mechanisms of Interference**

- Sodium and water retention
- Activation of the sympathetic nervous system
- Activation of the renin–angiotensin system
Commonly Recognized Substances Impeding Blood Pressure Control

- Non-steroidal anti-inflammatory agents
- Sympathomimetic agents
  - decongestants, diet pills, cocaine
  - methylphenidate, amphetamine salts
- Alcohol
- Corticosteroids
- Cyclosporine, tacrolimus
- Erythropoietin stimulating agents
- Estrogens (including oral contraceptives)
- Migraine medications
- Natural licorice

Less-Commonly Recognized Substances Impeding Blood Pressure Control

- Neurologic and psychiatric agents
  - Tricyclic antidepressants, SNRIs (e.g. venlafaxine),
  - Modafinil
- Herbal compounds
  - Ma huang (ephedra), bitter orange, blue cohosh, ginseng, guarana
- Vascular endothelial growth factor inhibitors
  - Bevacizumab
  - Sorafenib
  - Sunitinib

VEGF Inhibitors and Hypertension: Potential Mechanisms

Granger, J. P. Hypertension 2009;54:465-467

Treatment of Resistant Hypertension: 2008 AHA Statement

- Non-Pharmacologic Recommendations
- Pharmacologic Recommendations
  - Withdrawal or down titration of interfering substances
  - Use of a long-acting thiazide diuretic (i.e. chlorthalidone)
  - Combine agents with different mechanisms of action
  - Triple regimen of ACE inhibitor or ARB, calcium channel blocker, and thiazide diuretic

Treatment of Resistant Hypertension: 2008 AHA Statement

- Addition of mineralocorticoid receptor antagonist
- Use of loop diuretic in patients with CKD (creatinine clearance <30 ml/min)
- If blood pressure controlled consider adjustment of the treatment regimen to maintain control but with use of fewer medications and/or with use of a regimen that minimizes adverse effects
- Need for additional knowledge (research) to identify and effectively treat these patients

Diuretics and Their Primary Sites of Action

Hypertension. 2008;51:1403-1419
**Thiazide Diuretics**

- Excellent in combination with other agents
- Have been considered generally interchangeable
- Same pharmacologic effects
- Appropriate dose adjustment required
- Equivalent clinical efficacy?
- Different pharmacokinetics and subsequent pharmacodynamics

**Common Thiazide Diuretics**

<table>
<thead>
<tr>
<th></th>
<th>Absorption</th>
<th>% (hr)</th>
<th>Relative potency</th>
<th>Elimination</th>
<th>Anti-hypertensive dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>~45%</td>
<td>~47</td>
<td>1</td>
<td>65% R 10% H 35% U</td>
<td>12.5-25mg po once daily</td>
</tr>
<tr>
<td>HCTZ</td>
<td>~70%</td>
<td>~2.5</td>
<td>1</td>
<td>R</td>
<td>12.5-50mg po once daily</td>
</tr>
<tr>
<td>Indapamide</td>
<td>~83%</td>
<td>~24</td>
<td>26</td>
<td>&gt;95% H</td>
<td>1.25-5mg po once daily</td>
</tr>
<tr>
<td>Metolazone</td>
<td>~44%</td>
<td>6-5</td>
<td>10</td>
<td>85% R, 10% H, 5% U</td>
<td>2.5-10mg po once daily</td>
</tr>
</tbody>
</table>

* Dose dependent. HCTZ= Hydrochlorothiazide


**Are All Thiazides Equal?**

Chlorthalidone versus hydrochlorothiazide

- Half-life, duration of action
- Less braking phenomenon?
- ALLHAT, MRFIT versus ANBP2
- 24-hour ambulatory blood pressure comparison (Ernst et al. Hypertension. 2006;47:352-358.)

**Antihypertensive Effects of Hydrochlorothiazide versus Chlorthalidone on Blood Pressure**

- Mean change from week 0 to week 8 in average hourly ambulatory systolic BP.


**Antihypertensive Efficacy of HCTZ as Evaluated by ABPM**

- Reduction in BP (mm Hg)

Dose Response Curve of HCTZ as Evaluated by ABPM

Thiazide Diuretics
- Hypokalemia
  - Dose related
  - May affect clinical outcome
    - SHEP subanalysis
      - Participants who had hypokalemia after 1 year of treatment with a low-dose diuretic did not experience the reduction in cardiovascular events achieved among those who did not have hypokalemia

Inhibitors of Renal Epithelial Na⁺ Channels (K⁺ sparing diuretics)
- Triamterene and amiloride
  - Employed for antikaluetic actions
  - Generally poor antihypertensives when used alone (particularly triamterene)
  - Secreted into proximal tubule blocking Na⁺ channels in late distal tubule and collecting duct

Inhibitors of Na⁺/K⁺/2Cl⁻ Symporter (Loop Diuretics)
- Primary site of action: thick ascending limb
  - Site of greatest Na⁺ capacity (25% of filtered Na⁺ load)
  - Nephron segments past this site do not possess reabsorptive capacity to reabsorb this rejectate
  - Mechanism of action: inhibitors of Na⁺-K⁺-2Cl⁻ symporter
  - Effective despite low GFRs
    - Highly protein bound and not filtered into tubules
    - Efficiently secreted by organic acid transport system into proximal tubule gaining access to site of action

Loop Diuretics
- Antihypertensive mechanism: uncertain
- Do not have the demonstrated CV effects as the thiazide diuretics (studies not conducted)
- Particularly useful in low GFR states where thiazide diuretics may not be effective
- Generally need to be dosed twice daily (exception torsemide) when used for hypertension
Aldosterone Receptor Antagonists

- Aldosterone cause Na⁺ and water retention and increase K⁺ and H⁺ excretion
- Aldosterone antagonists competitively inhibit binding of aldosterone to these receptors
- Clinical efficacy is in part a function of endogenous levels of aldosterone

Aldosterone Receptor Antagonists

- Renewed interest in resistant hypertension
  - “Spironolactone: an old friend rediscovered” (Sica DA, Journ Clin HTN 2006;8:467-69.)
    - Slow onset, but long duration of action
    - 25-50mg daily shown effective in resistant hypertension
    - Effective even when plasma aldosterone levels normal
    - Strong additive effects with other agents


- Adverse Reactions
  - Serious hyperkalemia (> 6.0mmol/L): 5%
  - Renal insufficiency
  - Gynecomastia/breast pain (10% spironolactone)
  - Impotence, decreased libido, hirsutism, menstrual irregularities, breast cancer? (spironolactone)
  - GI side effects (gastritis, ulcerations)
  - Rash


- Listed contraindications (eplerenone)
  - Serum potassium >5.5 meq/L at initiation
  - Creatinine clearance ≤ 30 ml/min in any patient or < 50 ml/min if being used for HTN
  - Concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir
  - Type 2 diabetes with microalbuminuria
  - Serum creatinine >2.0 mg/dl (males) or >1.8 mg/dl (females)
Other Pharmacologic Considerations
When Treating Resistant Hypertension

- Within class half-lives
  - Losartan versus others
  - Bisoprolol versus others
- Ancillary properties of agents within a class
  - Beta-blockers
  - Chronotherapy
  - Bedtime administration
    - Calcium channel blockers
    - Rebound effect of clonidine
    - Consider patches

Less commonly used Agents

- Minoxidil
  - Need for concurrent diuretic and beta-blocker
- Reserpine
  - Well tolerated in low doses
  - Was often an add-on therapy in older trials including ALLHAT
  - Hydralazine
    - Cochrane review concluded insufficient evidence to support any effects long-term on systolic or diastolic blood pressure versus placebo

Prevalence, Treatment, and Control of Hypertension

Cochrane Database Syst Rev. 2010; Aug4;(8)CD004934

Percent of U.S. Adults

- Hypertension
- Treatment
- Control


Are there other approaches that may be useful to guide antihypertensive therapy in uncontrolled hypertension?

- Noninvasive hemodynamic testing
- Targeting of selected genetic polymorphisms
- Age/race profiling
- Plasma renin activity guided therapy
The Laragh Hypothesis I

Normal blood pressure is sustained by the close interaction of two factors:

1. The body sodium-volume content (V)
2. The plasma renin-angiotensin system (R)

Under normal circumstances this interaction works well. The blood pressure will not rise when body sodium-volume increases, since it leads to a prompt suppression of renin release by the kidneys. This results in a vasodilation which accommodates for the volume increase and keeps the blood pressure unchanged.

Laragh JH & Sealey JE, Am J Hypertens. 2011;24:1164-80

The Laragh Hypothesis I (continued)

Conversely, if the body sodium-volume falls, the kidneys reactively increase the plasma renin secretion. This results in increased arteriolar vasoconstriction which reduces the capacity of the arterial tree and keeps the blood pressure unchanged.


The Laragh Hypothesis II

According to this model, hypertension develops in three situations:

1. V hypertension

Low renin or V hypertension occurs when the body sodium-volume content increases but cannot be offset by a concomitant fall in ambulatory plasma renin activity (PRA), because PRA is maximally suppressed (PRA < 0.65 ng/ml/hr)

Laragh JH & Sealey JE, Am J Hypertens. 2011;24:1164-80

The Laragh Hypothesis II (continued)

2. R hypertension

Renin dependent or R hypertension, occurs when the plasma renin activity becomes too high for the existing body sodium-volume content (PRA ≥ 0.65 ng/ml/hr)

3. V + R hypertension

The combination of sodium-volume and renin dependent hypertension occurs when the body sodium-volume content increases but ambulatory PRA cannot fall sufficiently (PRA ≥ 0.65 ng/ml/hr)

Laragh JH & Sealey JE, Am J Hypertens. 2011;24:1164-80

Categories of Antihypertensive Drugs

**THE ANTI-V DRUGS**

(Natruretic drugs)

- Reduce body sodium-volume content
- Aldosterone receptor blockers
- Sulfonamide diuretics
- Calcium channel blockers (CCBs)
- Alpha adrenergic blockers

**THE ANTI-R DRUGS**

(Anti-renin-angiotensin system drugs)

- Block or suppress plasma renin-angiotensin vasoconstrictor activity
- ACE inhibitors (ACEIs)
- Angiotensin receptor blockers (ARBs)
- Direct renin inhibitors (DRIs)

**R1**: Drugs that block the renin-angiotensin system

- Converting enzyme inhibitors (ACEIs)
- Angiotensin receptor blockers (ARBs)
- Direct renin inhibitors (DRIs)

**R2**: Drugs that suppress renin secretion

- Beta adrenergic blockers
- Centrally acting alpha agonists
- Reserpine, methyl DOPA

Using Plasma Renin Activity (PRA) to Guide Treatment Decisions

- **PRA < 0.65 ng/ml/hr**
  - Add or increase anti-V drug, consider stopping anti-R drug
- **PRA > 0.65 ng/ml/hr - < 6.5 ng/ml/hr**
  - If on anti-R drug, add anti-V drug (if anti-R drug maximized)
  - If on anti-V drug, add anti-R drug
- **PRA > 6.5 ng/ml/hr**
  - Add or increase anti-R drug, consider stopping anti-V drug

Prediction of Treatment Response to Beta-blocker and Thiazide Diuretic

- Randomized clinical trial of 363 patients with untreated hypertension
  1. Initial randomization (monotherapy)
     - 50-100 mg atenolol (A), OR
     - 12.5-25 mg hydrochlorothiazide (H)
  2. Second phase (add-on therapy)
     - H added to A patients, OR
     - A added to H patients

Turner et al, Am J Hypertens 2010; 23:1014-22

SBP Response to Atenolol and Hydrochlorothiazide by Renin Percentile

- 73 outpatients with uncontrolled hypertension (SBP > 140, DBP > 90 on one or more drugs)

Baseline 1 Year
| SBP (mmHg) | 163 ± 3 | 140 ± 2 |
| DBP (mmHg) | 95 ± 1  | 84 ± 1  |
| # Drugs    | 2.1     | 1.5     |

Blumenfeld JD, Laragh JH, Am J Hypertens 1998; 11:694-6

PRA Guided Treatment of Resistant Hypertension

- Randomized evaluation of renin-test guided or clinical hypertension specialist care (n=84 on average of 3 medications)
- Renin-test guided therapy involved:

<table>
<thead>
<tr>
<th>PRA (ng/mL/hr)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.65</td>
<td>Subtracting anti-R drugs, and adding anti-V drugs if necessary</td>
</tr>
<tr>
<td>0.65-6.5</td>
<td>Adding either an anti-R or anti-V drug, whichever was missing</td>
</tr>
<tr>
<td>&gt; 6.5</td>
<td>Subtracting anti-V drugs, and adding anti-R drugs if necessary</td>
</tr>
</tbody>
</table>


Greater rates of BP control (74% vs. 59%)
Opportunity to Streamline Therapy

Control Rates by Strategy

- Retrospective analysis of 1,096 patients from the Genetic Epidemiology of Responses to Antihypertensives (GERA) study
  - Thiazide diuretic for all
  - Age/race criteria
  - Plasma renin activity

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Overall</th>
<th>Black subjects</th>
<th>White subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretic</td>
<td>53.8</td>
<td>55.2</td>
<td>52.4</td>
</tr>
<tr>
<td>Age/race</td>
<td>61.3</td>
<td>55.2</td>
<td>67.1</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>69.4*</td>
<td>62.1**</td>
<td>76.3*</td>
</tr>
</tbody>
</table>

* p<0.001 vs. other strategies
** p<0.02 vs. other strategies

Plasma Renin Determination

Current Status

No specific preparation needed
- Regular dietary habits maintained
- Antihypertensive treatment not altered
- Standard blood draw (EDTA Vacutainer)
- Centrifuged on the desk top
- Frozen samples sent to laboratory
- Cost of $30 reimbursable (MediCare Clinical Laboratory Fee Schedule)

How to account for current ACEi or ARB Therapy

Effective PRA (ePRA)

\[ ePRA = PRA \times 0.1 \]

Summary

- All thiazide diuretics are not equal
- All loop diuretics are not equal
- Expanded role for mineralocorticoid receptor antagonists
- Ancillary and within class differences of antihypertensive agents should be considered
- Methods such as PRA guided therapy can enhance blood pressure control
- Need for further research