How to Manage Side Effects of Antihypertensive Medications

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Agenda

- Thiazide-related hyponatremia
- Gout occurring on thiazide
- Nocebo effects
- Erectile dysfunction
- ACE inhibitor cough and angioedema
- Calcium blocker related edema
- Praising Prinzide: our flagship medication

Thiazide Hyponatremia Case

A 74 year old female with controlled hypertension on lisinopril/HCTZ 20/25 mg daily has a serum sodium of 130 on routine surveillance screening. You should advise her to:
A. Change to lisinopril 20 mg daily
B. Maintain lisinopril/HCTZ 20/25 mg daily
C. Reduce lisinopril/HCTZ to 10/12.5 mg daily
D. Stop lisinopril/HCTZ
E. Take salt tablets

Thiazide-Related Hyponatremia

- Most common electrolyte abnormality in the SHEP trial with chlorthalidone (CTD) 25mg, age ≥ 60, was hyponatremia
  - 1 year rate of K < 3.2 was 1.0%
  - 1 year rate of Na ≤ 130 was 1.8%
- Highest risk group: frail elderly women
- Not dose related

Management of Hyponatremia

- Asymptomatic Na 125 ± 5 associated with falling
- Preexisting asymptomatic hyponatremia risks symptomatic hyponatremia
- Consider differential diagnosis of hyponatremia: dehydration, fluid overload, NSAIDs, SSRIs, CNS and pulmonary disease
- Avoid excessive water drinking
- Stop thiazide for associated Na less than 130
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Thiazide and Gout

- Prospective Normative Aging Study, >30,000 human years: rate of gout was 7%/year in 1.8% who had urate levels ≥ 9 mg/dl
- HDFP study on chlorthalidone 25mg: 18 dropouts out of 3693 patients over 5 years, 0.5%
- Hypertension, weight gain, and furosemide are more strongly related to gout than thiazide
- Hyperuricemia with HCTZ is dose related
- Intercritical gout more than 1 year in 40%; 7% had no recurrence in >10 years

Cumulative incidence of gouty arthritis by prior urate levels. The numbers refer to the number of examination intervals for each group.

Management Options for Hypertensive Patients With Acute Gout Taking Thiazide Based on Clinical Context

Hypertension controlled on 1 or 2 medications:
Attack of gout, 0 or 1 prior attacks in past year
Lifestyle measures
Consider alternative hypertensive drug if serum uric acid > 6mg/dL (not taken during attack)

Attacks of gout, ≥ 2 prior attacks in past year
Lifestyle measures
Change to alternative antihypertensive drug

Hypertension controlled on ≥ 3 medications
Attack of gout, 0 or 1 prior attacks in past year
Lifestyle measures
Thiazide continuation with consideration of dose reduction
Consider pharmacologic antihyperuricemic therapy, ie, allopurinol, if serum uric acid > 6mg/dl (not taken during attack)

Hypertension controlled on ≥ 3 medications
Attack of gout, ≥ 2 prior attacks in past year
Lifestyle measures
Consider alternative antihypertensive drug if serum uric acid > 6 mg/dl (not during attack)
Consider pharmacologic antihyperuricemic therapy, ie, allopurinol and thiazide continuation
Case of Thiazide and Gout

A 74 year old male with controlled hypertension on prinzide 20/25mg x 2, amlodipine 10mg, and terazosin 10mg HS has a second episode of acute podagra. You should advise:

- Stop prinzide and switch to lisinopril 40mg plus furosemide 20mg bid
- Reduce prinzide to 20/25g x 1 and consider adding spironolactone 12.5g if followup blood pressures are elevated
- Add allopurinol following gout attack
- Stop prinzide, increase terazosin to 20mg hs, and consider adding atenolol

Thiazide and Quality of Life

- TOMHS: 8 QOL domains; chlorthalidone 15mg = placebo
- ALPINE: no difference in sexual satisfaction thiazide vs candesartan
- SHEP: sexual problems, thirst, nocturia chlorthalidone 25mg = placebo
### Frequency (%) of Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo</th>
<th>HCTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Urination</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2-11.8</td>
<td>1-5.9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>7-17.6</td>
<td>5.9-10.3</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stress Reaction</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>


### Thiazide Myths Exposed

- Significant cross reactivity with sulfa antibiotics has not been demonstrated; sulfa allergic patients have the same mildly increased reactivity to penicillin and thiazide (NEJM 2003;349:1628-35)
- Thiazide is first line treatment for calcium kidney stones due to idiopathic hypercalciuria and also treats idiopathic calcium lithiasis; avoid thiazide with hyperparathyroidism (raises serum Ca)
For Mild HCTZ Intolerance……

Such as dizziness, mild rash or phototoxicity, switch to thiazide-like….
- Chlorthalidone 12.5 – 25 mg
- Indapamide 1.25 – 2.5 mg

For hyponatremia (sodium < 130) or GFR < 30 cc/min, consider furosemide BID

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Nocebo Effects
- Placebo “I will please”
- Nocebo “I will harm”
- Both are effects of suggestion, expectation
- 25% receiving placebo report adverse effects mostly headache, nausea, drowsiness, fatigue, and insomnia
- One case of hypervagotonia caused idioventricular rhythm with placebo
THIS MEDICINE MAY CAUSE DIZZINESS, LIGHT-HEADEDNESS, OR FAINTING. DO NOT DRIVE, OPERATE MACHINERY, OR DO ANYTHING ELSE that could be dangerous until you know how you react to this medicine. Alcohol, hot weather, exercise, fever and certain medicines (such as barbiturates and narcotics) can increase these effects. To prevent them, sit up or stand slowly, especially in the morning. Also, sit or lie down at the first sign of dizziness, lightheadedness, or weakness. THIS MEDICINE MAY CAUSE increased sensitivity to the sun. Avoid exposure to the sun or sunlamps until you know how you react to the medicine. Use a sunscreen or protective clothing if you must be outside for a prolonged period.

Interactive Question

Is this the package insert for:
A. Arsenic
B. Mustard gas
C. Hydrochlorothiazide

Managing Nocebo Effects

- Identify patients at risk
- Physician/patient collaboration
- Step 1: Try a subtherapeutic dose
- Step 2: Reattribute nonspecific side effects
- Goal is to manage side effects, not to eliminate them
- It takes PHYSICIAN COMMITMENT
Case Study

65 year old male with long standing anxiety disorder on paroxetine (Paxil) intolerant to HCTZ due to mouth dryness, also intolerant to atenolol with tremors, and both lisinopril and nifedipine with fatigue was referred to Hypertension Clinic because of refractory hypertension due to medication intolerance.

Case Study

His psychiatrist attributed these symptoms to his underlying anxiety disorder. Paroxetine and bupropion (wellbutrin) were nonefficacious, but clonazepam (klonopin) led to a reduction in somatic complaints. HCTZ was successfully reinitiated, and in combination with lisinopril and atenolol led to control of his hypertension.
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Erectile Dysfunction

- Primary determinants are age and comorbidities
- Weight loss and exercise improve sexual function: TAIM, JAMA study, JCH study
- TOMHS: E.D. proportional to age and systolic pressure
- TOMHS: no change in E.D., CTD 15 mg vs placebo at 4 years
- SHEP: no change in sexual function CTD 25mg vs placebo

Beta-blockers and Report of ED

- % of patients reporting ED
- Blinded
- Knew drug no SE
- Knew Drug and SE
- P<0.05
- P<0.01
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Case of Lisinopril and Cough

A 52 year old female with controlled hypertension on prinzide 20/25mg develops persistent dry cough, bothersome to family. There is no history of post nasal drip, GERD, or asthma. You should advise:

A. Reduce prinzide to 10/12.5mg daily
B. Try cromolyn inhaler and iron 325 mg daily
C. Change prinzide to HCTZ 50mg, then consider adding losartan
D. Empiric trials of nasarel, chlortrimeton, then omeprazole
ACE Inhibitor Cough

Incidence 5-40%; not dose related; higher rate in females, blacks, asians
Cough characteristics not helpful in diagnosis (may be productive)
Timing: within a week to up to 6 months
Resolution: 1-4 days, up to 4 weeks
Pathophysiology: Bradykinin accumulation; no pulmonary dysfunction
Things that don’t work: iron, NSAIDs, cromolyn
Consider rechallenge

ACE Inhibitor Cough

- Not dose related
- Consider other cough etiologies: post nasal drip, GERD, asthma, heart failure, seasonal viral disease
- ACE inhibitors are preferred over ARBs (losartan) for patients with CAD and high CVD risk (ALL study)

Proportions of people reporting one or more symptoms attributable to treatment (treatment minus placebo, with 95% confidence interval) according to category of drug and dose as a proportion of standard

Law et al. BMJ 2003;326:1427-34
ACE Inhibitor Angioedema

- 0.3% nonblacks, 0.7% in blacks: ALLHAT
- Idiopathic angioedema is an ACE inhibitor contraindication
- Rarely can cause upper airway obstruction and abdominal pain
- Can change to an ARB: losartan
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Dear Dr. Handler,

Again I request another pill to replace “amlodipine” to eliminate the swelling of my ankles. Please! Summer is coming soon and my capri pants will not cover my swollen ankles.

Edith Wins, 94 years old

Calcium Blocker Edema Case

A 67 year old female with controlled hypertension on prinzide 20/25mg x 2, amlodipine 10mg, and atenolol 25 mg develops moderately bothersome 1+ bilateral pedal edema. You should advise her to:
A. Change prinzide to lisinopril 40mg plus furosemide 20mg daily
B. Switch amlodipine to long acting diltiazem 120mg daily
C. Advise sodium reduction to control edema
D. Reduce amlodipine to 5mg and advise daytime compression stockings

Pathophysiology of Calcium Channel Blocker Related Edema

- Not caused by fluid overload
- Not responsive to furosemide
- CCBs target precapillary arterioles to increase intracapillary pressure
- Intracapillary hypertension leads to fluid transudation into soft tissue and edema
- Edema is dependent, worse later in day and better in morning
Managing Calcium Channel Blocker Related Edema

1. Always consider other etiologies of edema, i.e., right heart failure due to sleep apnea, steroids, anegrilide, NSAIDs; heart, kidney, and liver failure
2. Lisinopril and losartan act on venular side of capillary circuit to reduce intracapillary pressure
3. Additional antihypertensive agents permit reduction of dose of CCB
4. Daytime compression stockings, leg elevation
5. Switch to another calcium blocker
6. Reassurance

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Simple algorithm: Prinzide First

- Prinzide followed by amlodipine, should control close to 80% of ALL our uncomplicated, DM, and CKD 1-3 patients with hypertension
- SIMPLICITY = PERFORMANCE
  - Fewer steps
  - Fewer pills
  - Faster control

Fixed Dose Combinations (FDCs): Rationale

- Improved control rates: 80% (ACCOMPLISH) vs 66% (ALLHAT)
- Reduced pill counts ("pill burden") improves patient adherence
- Reduced copays
- Balanced metabolic effects
- Reduced lab follow up, reduced venopunctures

STITCH TRIAL

- ACEI/thiazide ½ pill, advance to top dose
- Next, add and uptitrate CCB
- Comparator group: stepwise single drugs
- 6 month BP control: 64.6% vs 52.7%
Generic Prinzide Rx's by Month

BP Control and Prinzide Use

p = 0.03

SBP Reduction: Monotherapy ACEI Advance Vs Combination therapy with HCTZ
Questions?