Drug Induced Hypertension

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Disclaimer

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ARS1: Clinic Monday AM

A 41 yo woman you have followed for high BP on ACE/CCB Rx is 154/86 mmHg today. Her last three BP visits (over 1.5 years) have all been < 140 mmHg. What best explains this change?

• A) White Coat Effect
• B) Poor BP technique
• C) Dining at “The Real LeAnh” restaurant last night
• D) Dunno, that’s why I’m listening to this

Best recent review


Drug-Induced Causes

• Steroid-Related
  – 11 β-hydroxysteroid dehydrogenase inhibitors
  – Corticosteroids
  – Anabolic Steroids
• Sympathetic System-related
  – Sympathomimetic amines
  – Triyclic antidepressants
  – SSRI
  – MAO inhibitors
• NSAIDS including COX-2 inhibitors
• Erythropoietin
• Cyclosporin A (CNI)
• Oral Contraceptives
• Cocaine
• Ethanol
• VEGF Inhibitors
• Caffeine
• Weight loss/Appetite suppressants

D A S H

Townsend Disease a Month 1998;44:243-253
ARS Question

A 58 yo man, inpatient, is being treated for metastatic colon cancer. Shortly after his chemotherapy infusion he has a seizure. CT/MRI are both negative for brain mets. What best explains this?

- A. Hypertensive encephalopathy
- B. White matter hyperintensities
- C. Hypocalcemia
- D. Bevacizumab

TKI/VEGF antibodies

- Incidence of severe HTN (>200/>100) is 3-5x higher when compared with placebo arms in trials
- De-novo hypertension occurs in about 20% of people
- It can also happen with intra-ocular injection, but is low (<4%)

ARS Question

77 y/o woman with CKD, low grade lymphoma and hypertension. Medications: furosemide, ramipril
- eGFR 24 mL/min/1.73 m2
- Hb 9.7 gm/dl. Starts ESA therapy after iron stores found adequate. Hemoglobin rises to 12.0 in six weeks. Her blood pressures had been usually 126/76 mmHg, now they are 158/82 mmHg. What most likely accounts for this change?

- A) Prednisone
- B) NSAIDs
- C) Erythropoietin
- D) Paraneoplastic vasoconstrictor

ESAs and Hypertension
Cardiovascular Effects in a Sports Doping Model

Proposed Mechanisms

- Oxidative stress
- Intracellular reactive oxygen species
- Reduced NO synthesis
- NO resistance
- PGF-α and thromboxane
- Endothelin-1

Reports both for and against a role for each of these in direct EPO-mediated vasoconstriction and hypertension—is there a “dose-response” effect?

Peginesatide

Table IV: Time to First Event Analysis—MACE events

Overall AE HR 1.31 (99% CI 1.14–1.49) in CKD patients

Cocaine

- Massive increase in sympathetic nerve activity
  - Increases catecholamine release
  - Blocks neuronal reuptake of norepinephrine
  - Lasts minutes to a few hours
- Acute effects
  - Hypertension
  - Tachycardia

- Chronic Hypertension
  - Only in the setting of CKD
- Treatment
  - Sedatives
  - Alpha blockers
  - Verapamil
  - Avoid beta blockers
  - Create unopposed alpha-adrenergic stimulation
  - Associated with coronary vasoconstriction

Methamphetamine

- Massive increase in sympathetic nerve activity
  - Increases catecholamine release
    - Primarily norepinephrine and dopamine
    - Less expensive than cocaine
    - Lasts hours to days
- Acute effects
  - Hypertension
  - Tachycardia

- Chronic Hypertension
  - Chronic use causes hypertensive CKD
- Treatment
  - Sedatives
  - Alpha blockers
  - Verapamil
  - Avoid beta blockers
  - Create unopposed alpha-adrenergic stimulation
  - Associated with coronary vasoconstriction

Lange NEJM 2001;345:351-358
• Variable hypertensive response
  – Severe hypertension intravenously
  – Isolated cases with nasal or ocular use
  – Not related to common polymorphisms of alpha receptor
  – Combination with beta blocker could result in unopposed alpha adrenergic vasoconstriction

Buscher R, et al JPET 291(2);1999: 793-798

Dietary Supplements
• Herbal products
  – Anecdotal reports
  – Ingredients may be unknown
  – Be suspicious in patients with resistant hypertension
  – Stop all supplements
    • Observe BP
    • If improvement, may consider systematically resuming sequentially
  – Ephedra alkaloids increase BP
    • banned in US

ARS Question
• A 27 yo woman is sent to you by her GP for new onset hypertension. You notice her heart rate is 104 bpm, and seated BP is 134/92 mmHg. Which of the following best explains this?
  • A. Cocaine usage
  • B. Naproxen usage
  • C. Venlafaxine usage
  • D. Acai berry extract usage

Antidepressants
• MAO Inhibitors
  – Ingestion of tyramine
  – Combination with buspirone (serotonin receptor agonist
• Tricyclics
• Serotonin reuptake inhibitors
• Mixed serotonin/norepinephrine uptake inhibitors

NSAIDs
• NSAID users have a 40 % increased risk of hypertension compared to non-users
  – About 5 mmHg
  – Likely related to COX-2 inhibition
    • decreases sodium excretion
    • increases intravascular volume
  – Elderly
  – Pre-existing hypertension
  – Salt sensitivity
  – CKD
  – Reno-vascular hypertension
• Treatment
  – Discontinue or decrease dose
  – Calcium channel blockers
  – Diuretics

Source: Townsend chapter 149  NSAIDS/Coxibs/Angiogenesis inhibitors
ARS - 3

- A 22 year old man has a BP of 154/72 mmHg
- He is well appearing, 1.8 meters tall and 90 kg in weight (BMI = 27.8 kg/m²)
- He is untreated (no meds)
- EKG has voltage criteria for LVH
- Upper arm circumference is 44 cm (normal is about 34 cm)

ARS - 3

- What would you do next?
  - A 24 hour ABPM
  - B Serum aldosterone, plasma renin activity
  - C Home BP monitoring
  - D Ask about his hobbies and passions

ARS – 3

- You discover he is a body builder and has participated successfully in regional competitions. What would you do next?
  - A Measure urinary androgen metabolites
  - B Recommend antihypertensive medication
  - C Inquire about usage of supplements used in body building
  - D Refer to cardiology for LVH

Steroids

- Glucocorticoids
  - As many as 20 % develop hypertension
  - Dose dependent
  - Up to 15 mmHg SBP
  - More often in elderly
- Mineralocorticoids
  - Hypokalemia
  - Metabolic alkalosis
- Treatment
  - Discontinue or decrease dose
  - Calcium channel blockers
  - Diuretics

Calcineurin Inhibitors

- Cyclosporine and Tacrolimus
  - Dose dependent
  - Increases with age
  - Exacerbated by CKD
  - Responds to withdrawal or decreased dose
  - May not completely resolve
  - Often respond to calcium channel blockers

Estrogens

- Contraceptives
  - About 5 % of patients
  - Dose dependent
  - At least 50 mcg of estrogen
  - 1-4 mg Progestin
  - Occasionally with low dose estrogen
    - Occasionally more severe
- HRT
  - Small increases in BP
  - Increased cardiovascular morbidity
  - No longer routinely recommended
Caffeine

- Effects on BP not well defined
- Meta-analysis of randomized controlled trials of coffee or caffeine
  - 16 studies with randomized, controlled designs
  - 1,010 subjects
  - Increase of 2.04 mmHg SBP
  - Increase of 0.73 mmHg DBP
  - Blood pressure elevations induced were larger with caffeine (410 mg/day) than with coffee (725 mL/day)
  - Effects of coffee and caffeine on heart rate not significant


Heavy Metal Exposure

- Lead
  - Most data from epidemiologic studies
  - High incidence of hypertension in exposed patients
  - Even with low blood levels (<40 mcg/dl)
  - Associated with both SBP and DBP
  - No data on chelation
- Arsenic and Cadmium exposure may also be associated with hypertension

HAART for HIV

- Insulin resistance
  - More common with first generation protease inhibitors
- Small increases in SBP in some studies of HAART
  - Prevalence of hypertension in patients on HAART similar to that in HIV-negative controls


What they did

- Studied 33 participants; Age = 60 years; 28 ♂ and BMI of 27.8 kg/m²
- Randomized, Double-blind, Cross-over, Placebo
- Assessed ABPM before and after 2 weeks of Rx: either Pbo or acetaminophen 1gm TID
- Also assessed endothelial function, EPCs, Oxidative stress markers, renin and aldo, Pg’s and Tx’s

Sudano Circulation 2010

Does acetaminophen affect blood pressure in patients with coronary artery disease?
Take home ---

• These are clinically relevant doses of acetaminophen
• This is short term look-see, not an outcome trial, and in a specific population (CAD)
• But it does raise the query about presuming safety in the absence of overt contrary evidence

Drug Induced Hypertension

• Suspicion is key
  – Therapeutic drugs
  – Drugs of abuse
  – Dietary substances
  – Environmental toxins
  – Avoid need for invasive or costly evaluation
• Secondary form of hypertension
  – Associated with resistant hypertension
  – Hypertensive urgency or emergency
  – Modifiable
    • Stop drug or decrease dose
    • Specific therapies when unable to discontinue