AT THE FOREFRONT
UChicago Medicine

Not all cases of Hypertension and Hypokalemia are created equal

Learning Objectives

- What hypertensive medications can be used in pregnant patients
- Differential Diagnosis and Work-up for patients with Hypertension, Hypokalemia and Metabolic Alkalosis
- Review uncommon causes not typically seen, and discuss treatment options

History and Physical

Reason for Consultation/ Referral: Hypertension

HPI:

- 30 y/o female initially seen in 8/2014
- Patient was referred for further work-up and evaluation of her Hypertension
- She was being treated with Labetalol - as she was trying to get pregnant
- Pressures were in the 140-150s/90s mmHg with pulse in 70s BPM

History and Physical

PMH: None

PSH: No previous surgeries

Social History: No Tobacco, EtOH or Illicits

Family History: (+) Family History for Hypertension and Hypokalemia

History and Physical

Allergies:

NKDA

Home Meds:

Labetalol 100mg BID

Physical Exam:

Normal physical exam

Labs and Imaging

BMP:
Na 138, K 3.5, Cl 105, CO2 28, BUN 8, Cr 0.33

Aldosterone: 12 ng/dL

Renin: 0.7 ng/mL/hr

24 Hr Urine Aldosterone: Ordered, but patient did not do the test

TSH: 1.58 (0.450 - 5.500 uIU/mL)

Renal Duplex:

Right kidney was 10.9cm in length with echogenicity within normal limits and no hydronephrosis

Left kidney was 10.8cm in length with echogenicity within normal limits and no hydronephrosis

No evidence of renal artery stenosis

During Initial Hypertension Clinic Visit

Medications were adjusted:

- However, due to her trying to become pregnant , what medications would you consider using

ACOG Practice Guidelines:

HTN Medications safe for the treatment of chronic HTN during pregnancy include:

- **Labetalol - 2x daily, max dose of 2400mg per day**
- **Nifedipine ER - max dose of 120mg per day**
- **Methyldopa - 2-3x daily, max dose of 3000mg per day**
- **HCTZ - max dose of 25mg per day**

Labetalol and Nifedipine are preferred medications

Methyldopa and HCTZ are considered secondary options

New data continue to support that Amlodipine is safe

- Labetalol → was changed to Amlodipine 10mg q daily

Obstet Gynecol. January 2019; 133(1):215-219

Safety of Amlodipine in Early Pregnancy

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***Background*—**Amlodipine is used for the treatment of hypertension, but reports on its use in early pregnancy are limited.

***Methods and Results*—**In the present study, we recruited 231 women with chronic hypertension, including those who received amlodipine or other antihypertensives during early pregnancy, and investigated frequencies of morphologic abnormalities in their 231 offspring. Specifically, we evaluated 48 neonates exposed to amlodipine in the first trimester (amlodipine group, Group A), 54 neonates exposed to antihypertensives other than amlodipine (other antihypertensive group, Group O), and 129 neonates not exposed to antihypertensives (no-antihypertensive group, Group N). The number of morphologic abnormalities of offspring in each group were 2 in Group A (4.2%; 95% CI, 0.51–14.25); 3 in Group O (5.6%; 95% CI, 1.16–15.39) and 6 in Group N (4.7%; 95% CI, 1.73–9.85). The odds ratio of the primary outcome comparing Group A and Group O was 0.74 (95% CI: 0.118–4.621) and Group A and Group N was 0.89 (95% CI: 0.174–4.575).

***Conclusions*—**The odds of birth defects in Group A in the first trimester were not significantly different from those with or without other antihypertensives. **(*J Am Heart Assoc*. 2019;8:e012093. DOI: 10.1161/JAHA.119.012093.)**

Mito, A, et al. Safety of Amlodipine in Early Pregnancy. J Am Heart Assoc. 2019;8:e012093. DOI: 10.1161/JAHA.119.012093.)

Clinical Course

10/2014 - Patient became pregnant

4/2015 -Hypotension with BPs in the 100s/70-80s mmHg → Amlodipine was discontinued

6/2015 - Patient delivered via C-Section

12/2015 - Remained normotensive - remained off HTN medications

8/2016 - She had Wellness Check done thru her employer, labs were drawn
BMP: Na 141, **K 2.9**, Cl 100, **CO2 28**, BUN 5, Cr 0.64

9/2016 - Patient was seen by her PCP and was instructed to increase foods high in K. She was also re-referred back to Dr. Bakris due to HTN (BP in the 140s/ 90s mmHg) and electrolytes

Clinical Course - Continued

2/2017 - Seen in HTN Clinic, remained hypokalemic on repeat labs and BP remained in 140-150s/ 90s mmHg.

BMP: Na 141, **K 2.8**, Cl 99, **CO2 30**, BUN 8, Cr 0.6

Patient was started on **Amiloride 5mg** and PO KCl was increased to 40mEq BID

4/2017 - Repeat labs ordered and BP improved 130s/ 90s mmHg

BMP: **K 3.3**, **CO2 31**

Increased **Amiloride to 5mg BID** and increased PO KCl to 60mEq BID

6/2017 - Seen by PCP, BPs had improved to 110-120s/ 70s mmHg but no repeat labs

What would your differential diagnosis be for this patient (HTN, HypoK, Metabolic Alkalosis)?

Why would we have chosen to use Amiloride?

HTN, Hypokalemia and Metabolic Alkalosis

High Aldosterone:

Primary Hyperaldosteronism

Renal Artery Stenosis

Renin Secreting Tumors

Glucocorticoid Remediable Aldosteronism

Low/ Normal Aldosterone:

Liddle's Syndrome

Apparent Mineralcorticoid Excess

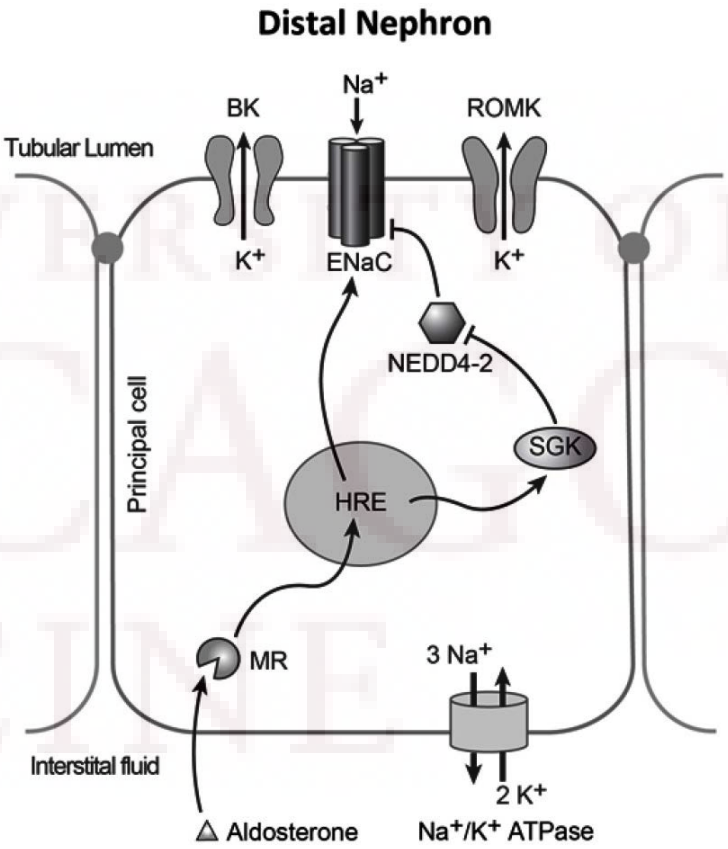
- Autosomal recessive inactivating mutation of 11β-hydroxysteroid dehydrogenase type 2 gene
- Inhibition of 11β-hydroxysteroid dehydrogenase type 2 by Licorice

Cushings

Congenital Adrenal Hyperplasia

Liddle's Syndrome

- Autosomal Dominant
- Gain of function mutations to subunits of the Epithelial Sodium Channel (ENaC)
- Results in inappropriately elevated sodium reabsorption in the distal nephron
- Genetic testing is the most reliable method for establishing the diagnosis (www.genetests.org)
- Treatment with Low Na diet and Amiloride or Triamterene

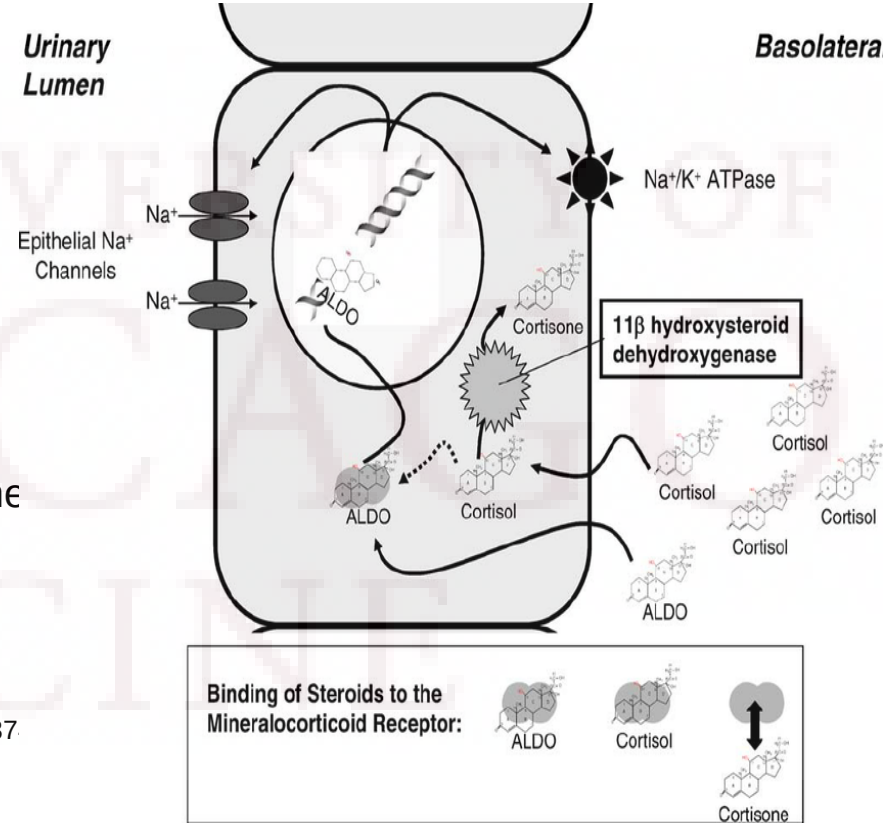


Enslow, BT. Integr Blood Press Control 2019 Sep 3;12:13-22. doi: 10.2147/IBPC.S188869.

Apparent Mineralcorticoid Excess

- **Genetic**
  - Autosomal Recessive
  - Inactivity mutation of 11β HSD2 gene
  - 11β HSD2 converts Cortisol → Cortisone
  - Aldosterone and Cortisol act on the Mineralcorticoid Receptor

- **Inhibition of enzyme**
  - Glycyrrhizic acid from the licorice root is the main active component of licorice
  - Metabolized to Glycyrrhetinic Acid
  - Glycyrrhetinic acid inhibits 11β HSD2



Rosskopf, D.Naunyn-Schmiedeberg's Archives of Pharmacology. March 2007. 37
6):429-69DOI: 10.1007/s00210-007-0133-2

Clinical Course - Continued

8/2018 - Patient was seen in HTN Clinic for follow-up

She had taken herself off the Amiloride and had restarted Amlodipine 5mg q daily - BP controlled in 120s/ 70-80s mmHg

BMP: **K 2.8** (on PO KCl of 40mEq in AM and 20mEq in PM)

Was restarted on Amiloride 5mg BID

9/2018 - Repeat labs ordered

BMP: Na 139, K 3.6, Cl 105, CO2 26, BUN 10, Cr 0.8

1/2019 - Patient was seen in HTN Clinic for follow-up

Had been trying to get pregnant again, although unsuccessfully - scheduled to see Fertility Specialist

Had again decreased her Amiloride to 5mg q daily

BMP: Na 140, **K 3.3**, Cl 100, **CO2 30**, BUN 12, Cr 0.8

Increased Amiloride to 5mg BID

Clinical Course - Continued

11/2019 - Patient was able to get pregnant and was being followed by OB/Gyn and PCP

What Category of Drug is Amiloride for Pregnant Patients?

8/2020 - Patient was seen in HTN Clinic for follow-up, because her pressures were poorly controlled (post-partum). BP 160s/ 90s mmHg on Labetalol. Not on Amiloride

BMP: Na 135, **K 3.1,** Cl 103, CO2 24, BUN 12, Cr 0.76

Her medications were adjusted and titrated over the next several months - with us settling on **Nifedipine ER 60mg q daily, Amiloride 20mg q daily, KCl 20mEq BID**

Until 3/2021 - Patient was seen in HTN Clinic due to having low BPs 100s/ 70s mmHg

BMP: Na 140, **K 3.9**, Cl 106, CO2 29, BUN 13, Cr 0.7

Medications adjusted - Holding Nifedipine for 2 weeks, Continue Amiloride 20mg

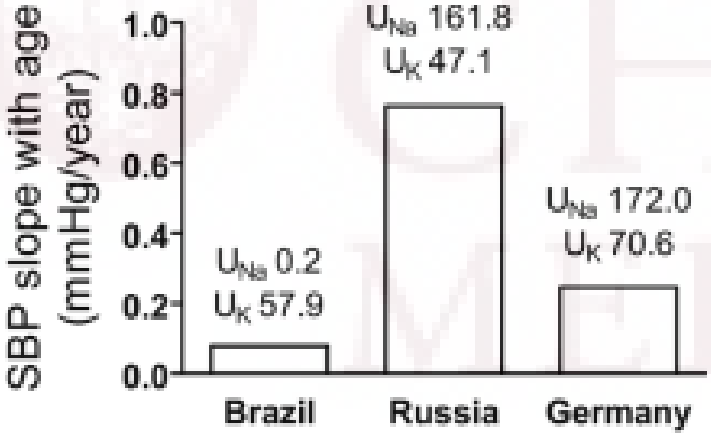
Patient also wanted to decrease KCl to 20mq q daily with Increased PO Foods high in K

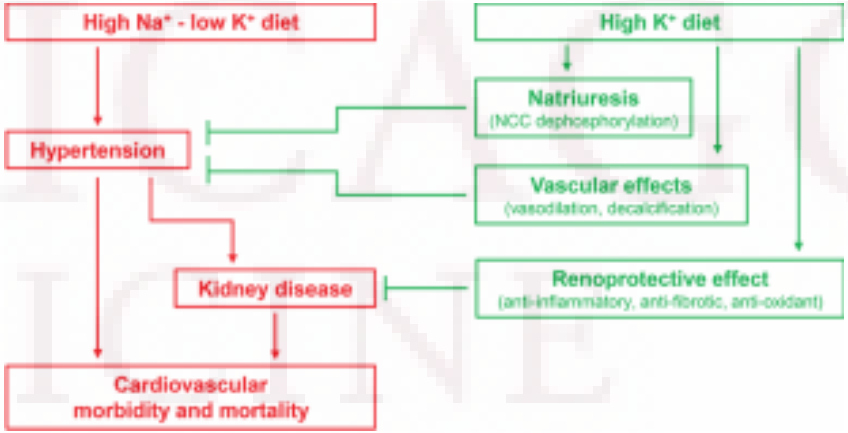
PDR

Amiloride is classified as **pregnancy category B**. There are no adequate and well-controlled studies in pregnant women. According to the manufacturer, the drug should be administered to pregnant women only when the potential benefits to the mother outweigh the potential risk to the fetus

Dietary Potassium in Blood Pressure Reduction

- In 1928, in Canadian Medical Association Journal there was anecdotal observation that K salts reduced BP, whereas Na salts increased BP
- Numerous studies have confirmed the negative effects of Na, and beneficial effects of K on BP and CV health
- More focus placed on decrease in dietary Na, compared to an increase in dietary K





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Gritter, M, et al. Role of Dietary K in Natriuresis, Blood Pressure Reduction, Cardiovascular Protection, and Renoprotection. Hypertension. 2019; 7: 15-23

References

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