(New) Drugs for the Management of Hypertension
March 9th, 2019

Guido Filler, MD, PhD, FRCPC
London, Canada

Pediatric Nephrology Seminar 2019
Disclosures

- I have no financial relationships to disclose relevant to my presentation
Objectives

• To review the resisting classes of antihypertensives
• To learn about newer developments in existing classes
• To learn about new potential targets
Which statement is correct?

1. Eplerenone is an Aldosterone antagonist
2. Bumetanide, furosemide, ethacrynic acid and indapamide are loop diuretics
3. All calcium channel blockers end with “ipine”
4. Ramipril has the same elimination as enalapril
5. Carvedilol is an alpha blocker
Existing Classes of Antihypertensives
What are the existing classes of HTN medications?

1. Diuretics
2. Calcium channel blockers
3. ACE inhibitors
4. Angiotensin II receptor antagonists
5. Adrenergic receptor antagonists
6. Vasodilators
7. Renin Inhibitors
8. Aldosterone receptor antagonists
9. Alpha-2 adrenergic receptor agonists
10. Endothelium receptor blockers
Diuretics
1. Diuretics

1. Loop diuretics
   1. Furosemide (up to 10 mg/kg/d)
   2. Ethacrynic acid

2. Thiazide diuretics
   1. Hydrochlorothiazide (0.5-2 mg/kg/d) and Chlorothiazide

3. Thiazide-like diuretics
   1. Chlorthalidone

4. Potassium sparing diuretics
   1. Amiloride (0.5-2 mg/kg/d – not licensed in children)
   2. Spironolactone (1-4 mg/kg/d)
   3. Eplerenone
Calcium Channel Blockers
2. Calcium Channel Blockers

1. Dihydropyridines
   1. Amlodipine (0.1 to 0.5 mg/kg/day)
   2. Cilnidipine
   3. Clevidipine
   4. Felodipine
   5. Isradipine
   6. Lercanidipine
   7. Levamlodipine
   8. Nicardipine
   9. Nifedipine (0.2-0.5 mg/kg/dose, max 10 mg)
   10. Nimodipine
   11. Nisoldipine
   12. Nitrendipine

2. Non-Dihydropyridines
   1. Diltiazem
   2. Verapamil
ACE Inhibitors
ACE Inhibitors

1. ACE inhibitors inhibit the activity of angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.

1. Captopril – indicated for infants, very short half-life
2. **Enalapril** – 100% renal elimination, 0.1-0.5 mg/kg/d
3. Fosinopril – could be eliminated completely by liver
4. Lisinopril
5. Moexipril
6. Perindopril
7. Quinapril
8. **Ramipril** – 60% renal and 40% faecal elimination, 0.1-0.5 mg/kg/d
9. Trandolapril
10. Benazepril

New Drugs for the Management of HTN
Angiotensin II Receptor Antagonists
4. Angiotensin II Receptor Antagonists

1. Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.

1. Azilsartan – approved 2011
2. Candesartan
3. Eprosartan
4. Irbesartan
5. Losartan – (0.7-1.4 mg/kg/d)
6. Olmesartan
7. Telmisartan
8. Valsartan
9. Fimasartan – approved 2010
Adrenergic Receptor Antagonists
5. Adrenergic Receptor Antagonists

1. Beta Blockers
   1. Acebutolol
   2. **Atenolol (0.3-1.3 mg/kg/d)**
   3. Bisoprolol
   4. Betaxolol
   5. Carteolol
   6. *Carvedilol (0.05-1 mg/kg/d) – 3rd generation*
   7. *Labetalol (0.2-1 mg/kg up to 40 or continuous infusion of 0.25-3 mg/kg/h iv)*
   8. Metoprolol (0.4-2.4 mg/kg/d)
   9. Nadolol (0.25-2.5 mg/kg/d)
   11. Oxprenolol
   12. Penbutolol
   13. Pindolol
   14. **Propranolol (0.5-16 mg/kg/d)**
   15. Timolol
5. Adrenergic Receptor Antagonists (2)

2. Alpha Blockers
   1. Doxazosin (for age 6-11 initially 500 mg, then 2-4 mg OD)
   2. Phentolamine
   3. Indoramin
   4. Phenoxybenzamine
   5. Prazosin (0.02-0.3mg/kg)
   6. Terazosin
   7. Tolazoline

3. Mixed Alpha + Beta Blockers
   1. Bucindolol
   2. Carvedilol (0.05-1 mg/kg/d)
   3. Labetalol (0.2-1 mg/kg up to 40 or continuous infusion of 0.25-3 mg/kg/h iv)
Vasodilators
6. Vasodilators

1. Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed, and even so are rarely given alone.

1. Sodium nitroprusside – for malignant hypertension (initially 0.3-0.5 mcg/kg/min IV, titrate every few minutes to 0.5-8 mcg/kg/min)

2. Hydralazine (0.1-0.5 mg/kg/dose IV q6-8 h)
Direct Renin Inhibitors
7. Direct Renin Inhibitors

1. Renin comes one level higher than angiotensin converting enzyme (ACE) in the renin–angiotensin system. Inhibitors of renin can therefore effectively reduce hypertension.

2. Aliskiren (developed by Novartis) is a renin inhibitor which has been approved by the U.S. FDA for the treatment of hypertension.

3. Not indicated for children
New Drugs for the Management of HTN

The Renin-Angiotensin-Aldosterone System (RAAS)

Liver secretes angiotensinogen

Kidney
Secretes renin in response to:
1. decreased arterial pressure in the kidneys
2. decreased sodium in the blood
3. increased sympathetic tone

Angiotensinogen

Angiotensin I

Angiotensin Converting Enzyme (ACE) converts Angiotensin I to Angiotensin II

Angiotensin II

Angiotensin II Receptors located in adrenal glands, vascular smooth muscle, the heart, and the brain

Angiotensin II Receptor Blockers (ARBs) block angiotensin II receptors

Angiotensin stimulates aldosterone secretion in the adrenal glands.
Aldosterone promotes sodium and fluid retention.

Angiotensin stimulates sodium and fluid retention in the kidneys

Angiotensin stimulates muscle hypertrophy and fibrosis in the heart

Angiotensin stimulates sympathetic outflow in the brain

Angiotensin stimulates vasoconstriction in blood vessels

ACE inhibitors block ACE

Aliskiren (Tekturna®) blocks renin

Liver

Lungs secrete angiotensin converting enzyme
Aliskiren in children

• Aliskiren is not approved for children! Product info: Safety and dosing for children 6-17 not established!

• Limited evidences:

• High prevalence of side effects in children

• Novartis terminated large RCT because of safety concerns and lack of efficacy

• For adolescents >50 kg: 150 mg OD, may increase to 300 mg OD
Combination Therapy of Aliskiren and ARB

DOI 10.1007/s00467-010-1702-z

BRIEF REPORT

Are we ready to use aliskiren in children?

Erin Elizabeth Kelland · Leanne Michelle McAuley · Guido Filler

Received: 20 August 2010 / Revised: 14 October 2010 / Accepted: 15 October 2010 / Published online: 11 December 2010
© IPNA 2010

Abstract The objective of this case series was to review the safety and efficacy of aliskiren in combination with losartan in pediatric chronic kidney disease (CKD) patients. This was a retrospective study in which the medical files of all patients who had received aliskiren were reviewed. Four patients were identified between 5 and 18 years of age who had received aliskiren and losartan for the reduction of refractory proteinuria. While proteinuria was reduced in all four of these patients by 45, 96, 53, and 64%, respectively, three patients experienced side effects requiring changes in the aliskiren dose. A significant side effect occurred in the patient with CKD stage 3 who suffered accelerated loss of RAS blockade [3]. The ONTARGET trial, however, shows that double RAS blockade can be associated with an increased risk for acute kidney injury and is now only recommended for proteinuria [4]. Angiotensin converting enzyme (ACE) inhibition results in an accumulation of renin and angiotensin I, which may cause “ACE escape” [5] with non-ACE conversion of angiotensin I to angiotensin II. This ACE escape was also demonstrated in the recent ESCAPE trial in children with chronic kidney disease (CKD) [6]. For angiotensin II receptor type I blockers (ARBs), a similar mechanism has been discovered, the “Aldosterone escape”, which leads to normal or even
Aldosterone Receptor Antagonists
8. Aldosterone Receptor Antagonists

1. Aldosterone receptor antagonists are not recommended as first-line agents for blood pressure, but spironolactone and eplerenone are both used in the treatment of heart failure and resistant hypertension.

1. Spironolactone
2. Eplerenone

Combination Therapy of with Eplerenone

• Chronic Allograft Nephropathy (IF/TA) is a major problem
• IF/TA is present in 53%–90% of protocol biopsy samples at 12 months post-transplant, and its severity correlates with renal dysfunction and proteinuria
• Paediatric data from a small RCT based on the positive effects of aldosterone/mineralocorticoid receptor blockade in an animal model
Combination Therapy of with Eplerenone

Combination Therapy of with Eplerenone


Plot A: Systolic BP (mmHg) vs. Time (months).
Plot B: Diastolic BP (mmHg) vs. Time (months).
Plot C: Serum Potassium (mEq/L) vs. Time (months).
Plot D: Serum Aldosterone (pg/ml) vs. Time (months).

Figure legend: The plots represent the effect of eplerenone treatment on blood pressure, serum potassium, and aldosterone levels compared to placebo. Solid line (●) indicates placebo and dashed line (○) indicates eplerenone treatment. The data are expressed as mean ± SEM.
Long-term eplerenone administration effect on renal function and tubulo-interstitial fibrosis. (A) Serum creatinine, (B) eGFR by the Zappitelli formula, (C) urinary albumin-to-creatinine ratio, and (D) percentage of tubulo-interstitial fibrosis assessed by morphometry analysis in placebo- (○) or eplerenone-treated patients (■). The data are expressed as mean±SD, except for urinary albumin-to-creatinine ratio expressed as median and 25th–75th percentiles. Alb/Cr, albumine/creatinine ratio; Ep0, eplerenone month 0; Ep6, eplerenone month 6; Ep12, eplerenone month 12; Ep24, eplerenone month 24; P0, placebo month 0; P6, placebo month 6; P12, placebo month 12; P24, placebo month 24.
Combination Therapy of Ramipril with 25 mg Eplerenone in a 7-year old with severe HUS
Alpha-2 Adrenergic Receptor Antagonists
9. Alpha-2 Adrenergic Receptor Agonists

1. Central alpha agonists lower blood pressure by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow. These alpha 2 receptors are known as autoreceptors which provide a negative feedback in neurotransmission (in this case, the vasoconstriction effects of adrenaline). Central alpha agonists, such as clonidine, are usually prescribed when all other antihypertensive medications have failed. For treating hypertension, these drugs are usually administered in combination with a diuretic.

1. Clonidine (<12 years: 5-10 mcg/kg/d PO in 2-3 divided doses, up to 25 mg/kg/d)
2. Guanabenz
3. Guanfacine – new indication for ADHD 2011, >12 years 1 mg QD
4. Metyldopa
5. Moxonidine
Endothelium Receptor Blockers
10. Endothelium Receptor Blockers

1. Bosentan belongs to a new class of drug and works by blocking the receptors of the hormone endothelium. It is specifically indicated only for the treatment of pulmonary artery hypertension in patients with moderate to severe heart failure.

2. Also leads to fall in systemic vascular resistance and mean arterial pressure.
New Drugs for the Management of HTN

**Endothelin Pathway**
- Pre-proendothelin → Proendothelin
- Endothelin-1
  - **ERA**
  - **ERA stimulator**
  - Endothelin receptor A
  - Endothelin receptor B

**Nitric Oxide Pathway**
- L-arginine → L-citrulline
- NO
  - sGC stimulator
  - cGMP
  - PDE-5
  - PDE-5 inhibitor

**Prostacyclin Pathway**
- Arachidonic acid → Prostaglandin I₂
- Prostacyclin → PGl₂
  - IP₂ agonist
  - IP₂ receptor
  - cAMP

**FDA Approved PAH Drugs**
- ERA
  - bosentan
  - ambrisentan
  - macitentan

- PDE-5i
  - tadalafil

- sGC stimulator
  - riociguat

- Prostacyclins
  - epoprostenol (IV)
  - iloprost (INH)
  - treprostinil (IV, SQ, INH, oral)

- IP₂ agonist
  - selexipag
Urapidil
1. Urapidil is a sympatholytic antihypertensive drug. It acts as an $\alpha_1$-adrenoceptor antagonist and as an 5-HT$_{1A}$ receptor agonist.

2. Unlike some other $\alpha_1$-adrenoceptor antagonists, urapidil does not elicit reflex tachycardia, and this may be related to its weak $\beta_1$-adrenoceptor antagonist activity.

3. Only available in Europe.
Novel ways to lower blood pressure
12. Novel ways to lower blood pressure

1. **SPYRAL trial**: Global Clinical Study of Renal Denervation With the Symplicity Spyral™ Multi-electrode Renal Denervation System in Patients With Uncontrolled Hypertension in the Absence of Antihypertensive Medications (SPYRAL PIVOTAL - SPYRAL HTN-OFF MED) – 433 patients - ClinicalTrials.gov identifier (NCT number): NCT02439749

2. **CALM-2 Study**: The MobiusHD is an investigational implant designed to lower blood pressure through a minimally-invasive procedure. The MobiusHD device is a self-expanding nitinol implant that is delivered intravascularly to the internal carotid sinus via the delivery catheter. – 300 patients - ClinicalTrials.gov identifier (NCT number): NCT03179800
Summary

- Most of the targets for blood pressure management are quite old concepts
- Direct Renin Antagonists have not been established in children
- Eplerenone may have a better side effect profile than Spironolactone
- Uradipil was promising and recent adult studies show that it is better tolerated than Nitroglycerine, but no paediatric data
1. Diuretics (2)

1. One of the earliest strategies involves changing the sodium balance
2. Thiazides since 1950ies
3. Mainstay of adult hypertension management
4. Decrease of extracellular volume
5. Decrease of cardiac output
6. Despite compensatory mechanisms of the body, antihypertensive effect is sustained
7. Not useful for advanced CKD
2. Calcium Channel Blockers (2)

1. Hass and Hartfelder reported Verapamil in 1962

2. Negative inotropic and chronotropic effects different from nitroglycerin, both on cardiomyocytes and smooth muscle cells

3. Reduction of the influx of \( \text{Ca}^+ \) into the cardiomyocytes

4. Many hormones increase intracellular \( \text{Ca}^+ \) concentrations, its inhibition results in vasodilation