The potential importance of antihypertensive properties of non-antihypertensive drugs in patients with prehypertension

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The mechanisms of blood pressure control, as well as, pathogenesis of prehypertension and hypertension are complex.

Many drugs which are non-classic antihypertensive drugs might affect different elements of prehypertension and hypertension pathogenesis and may lead to blood pressure reduction.

Antihypertensive properties of non-classic antihypertensive drugs

1. Anti-obesity drugs
2. Drugs used in uric acid lowering therapy
3. Anti-diabetic drugs
4. Calcimimetics
5. Phosphodiesterase type 5 inhibitors
Orlistat reduces lipase activity in duodenum
Orlistat

- 554 obese patients with hypertension were observed during 1 year
- Orlistat 3 x 120 mg vs placebo

↓ body mass by 2.7 kg

↓ SBP by 2.3 mmHg (0.9 mmHg/kg)

↓ DBP by 2.2 mmHg (0.8 mmHg/kg)

Orlistat

- Meta-analysis of 4 randomized, placebo-controlled trials with placebo last over 24 weeks involving 3,112 obese patients with hypertension
- Orlistat 3 x 120 mg
- ↓ body mass by 3.7 kg

↓ SBP by 2.5 mmHg (0.7 mmHg/kg)

↓ DBP by 1.9 mmHg (0.5 mmHg/kg)

Anti-obesity drugs

- **Orlistat** (available in Europe)
  - ↓ body mass by 3.7 kg
  - ↓ SBP by 2.5 mmHg (0.7 mmHg/kg of weight loss)

  *Siebenhofer A. et al. Cochrane Database Syst Rev. 2013:CD007654*

- **Phentermine and topiramate** (registered in the USA)
  - ↓ body mass by 10.2 kg
  - ↓ SBP by 9.1 mmHg (0.9 mmHg/kg of weight loss)


There are no studies concerning:

- **Locasterine** (serotonin 2C receptor agonist; registered in the USA)
- **Naltrexone/bupropion** (drug used to addiction treatment / antidepressant, available in Europe)
The antihypertensive effect of the low calorie diet and increased physical activity

- Meta-analysis of 25 randomized studies
- 4874 participants

↓ body mass by 5.1 kg
↓ SBP by 4.4 mmHg (0.9 mmHg/kg)
↓ DBP by 3.6 mmHg (0.7 mmHg/kg)

Neter J.E. et al. Hypertension 2003; 42: 878-884
In obese patients with hypertension, the reduction in blood pressure caused by orlistat is mainly associated with weight loss.

\[ \downarrow \text{SBP by 2.3 mmHg (0.9 mmHg/kg)} \]

\[ \downarrow \text{body mass by 2.7 kg} \]
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Purine metabolism

ATP + Ryb-5-P \rightarrow PRPP

PRPP synthetase

PRPP

amidoPRT

APRT

APRT

synthesis de novo

ATP - adenosine triphosphate; PRPP - 5-phosphoribosyl-1-pyrophosphate; amidoPRT - amidophosphoryltransferase; PRT - phosphoribosyltransferase; Ade-adenine; Xan-xanthine, Hypoxanthine, Gua-guanine

Xanthine oxidase

ALLOPURINOL

FEBUXOSTAT

URIC ACID

Purine nucleotides

Purine nucleotides
Drugs used in uric acid lowering therapy

- Randomized placebo controlled study with „cross-over” design
- 30 children with untreated hypertension aged 11-17 years and plasma uric acid concentration > 6 mg%
- Allopurinol 2 x 200 mg vs placebo during 4 weeks
- ↓ uricaemia by 2.7 mg/dL

Feig D. et al. JAMA 2008; 300: 924-932
Drugs used in uric acid lowering therapy

↓ 24h - SBP by 6.3 mmHg
(2.3 mmHg/mg/dl)

↓ 24h - DBP by 4.6 mmHg
(1.7 mmHg/mg/dl)

Feig D. et al. JAMA 2008; 300: 924-932
Drugs used in uric acid lowering therapy

- Randomized placebo controlled study
- 60 adolescents with prehypertension and obesity aged 11-17 years with plasma uric acid concentration > 5 mg%
- Allopurinol 200 mg or probenecid 1g vs placebo during 7 weeks
- Allopurinol or probenecid treatment leads to:
  - ↓ uricaemia by 2.5 mg/dL
  - ↓ 24h-SBP by 9.0 mmHg
  - ↓ 24h-DBP by 6.7 mmHg

Soletsky B. et al. Hypertension 2012; 60: 1148-1156
Drugs used in uric acid lowering therapy

- Data analysis from *UK Clinical Practice Research Datalink*
- Patients with hypertension in the age over 65 years
- 378 patients treated with allopurinol vs 378 untreated ones

  Allopurinol treatment leads to: ↓ SBP by 3.0 mmHg
  ↓ DBP by 3.3 mmHg

*Beattie C.J. et al. Hypertension 2014; 64: 1102-1107*
Drugs used in uric acid lowering therapy

- Meta-analysis of 10 prospective or retrospective clinical trials involving 738 patients with hypertension

Allopurinol: ↓ SBP by **3.3 mmHg**  ↓ DBP by **1.3 mmHg**

Drugs used in uric acid lowering therapy

- Meta-analysis of 15 randomized clinical trials

Allopurinol: ↓ SBP and ↓ DBP

Drugs used in uric acid lowering therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment $^a$</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>72 (67–78)</td>
<td>74 (69–80)</td>
<td>75 (69–80)</td>
<td>.87</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.4 (5.6–7.1)</td>
<td>6.2 (5.4–7.0)</td>
<td>6.6 (5.9–7.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Systemic vascular resistance index, (dyne s/cm$^5$)/m$^2$</td>
<td>2478 (2223–2731)</td>
<td>2473 (2232–2615)</td>
<td>2136 (2056–2228)</td>
<td>.03 $^b$</td>
</tr>
<tr>
<td>Total body water, L</td>
<td>27.8 (26.0–29.7)</td>
<td>28.0 (26.1–30.1)</td>
<td>28.1 (26.0–29.9)</td>
<td>.86</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL/h</td>
<td>1.9 (1.7–2.2)</td>
<td>2.1 (1.8–2.4)</td>
<td>1.4 (0.8–2.1)</td>
<td>.02 $^b$</td>
</tr>
</tbody>
</table>

Feig D. et al. JAMA 2008; 300: 924-932
Drugs used in uric acid lowering therapy

- Meta-analysis of 10 trials involving 670 patients
- Allopurinol: ↑ flow mediated vasodilatation (FMD)

Antihypertensive properties of non-classic antihypertensive drugs

1. Anti-obesity drugs
2. Drugs used in uric acid lowering therapy
3. Anti-diabetic drugs
   - Metformin
   - SGLT2 inhibitors (sodium-glucose cotransporter-2 inhibitors)
   - GLP-1 receptor agonists (glucagon-like peptide-1)
4. Calcimimetics
5. Phosphodiesterase type 5 inhibitors
Metformin reduces the gluconeogenesis in the liver and increases the insulin sensitivity in the skeletal muscles.
Metformin

- Meta-analysis of 28 randomized clinical trials involving 4113 non-diabetic subjects
- Metformin leads to ↓ SBP by 2.0 mmHg
- Metformin does not affect DBP
- In obese patients metformin causes ↓ SBP by 3.0 mmHg
- In patients with impaired glucose tolerance metformin causes ↓ SBP by 5.0 mmHg

Metformin

• Causes of antihypertensive effect:
  - weight loss
  - ↓ insulin resistance and ↓ insulinaemia (leading to sympathetic nervous system activity decrease and natriuresis increase)

Antihypertensive properties of non-classic antihypertensive drugs

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SGLTP 2 inhibitors (sodium-glucose cotransporter-2 inhibitors)

Filtered glucose > 180 g/d

↓ sodium-glucose cotransporter – 2 activity

- Canagliflozin
- Dapagliflozin
- Empagliflozin

Elimination of 80 g/d glucose in urine (loss of about 200 kcal/d)

Figure provided by Prof. Andrzej Więcek
SGLT2 inhibitors (sodium-glucose cotransporter-2 inhibitors)
Empagliflozin - EMPA-REG OUTCOME

↓ SBP by 4.2 mmHg

↓ DBP by 1.8 mmHg

SGLT2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)
Canagliflozin - CANVAS

↓ SBP by 3.9 mmHg

↓ DBP by 1.4 mmHg

SGLT2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)

• Meta-analysis of 27 randomized clinical trials involving 12960 patients (9 studies with canagliflozin, 12 studies with dapagliflozin, 3 studies with empagliflozin)

• SGLT2 inhibitors leads to: ↓ SBP by 4.0 mmHg
  ↓ DBP by 1.6 mmHg

SGLTP 2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)

• Meta-analysis of 6 randomized clinical trials with the ABPM use involving 2098 patients (1 study with canagliflozin, 3 studies with dapagliflozin, 1 study with empagliflozin, 1 study with ertagliflozin)

• SGLTP 2 inhibitors leads to: ↓ SBP by 3.8 mmHg
  ↓ DBP by 1.8 mmHg

SGLTP 2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)

Causes of antihypertensive effect:

• ↓ weight loss
• ↓ uricaemia
• ↑ natriuresis

SGLT2 inhibitors (sodium-glucose cotransporter-2 inhibitors) EMPA-REG OUTCOME

↓ body mass by ~ 2 kg

SGLTP 2 inhibitors (sodium-glucose cotransporter-2 inhibitors)

Causes of antihypertensive effect:
• ↓ weight loss
• ↓ uricaemia
• ↑ natriuresis

SGLTP 2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)
EMPA-REG OUTCOME

↓ uricaemia by ~ 0.4 mg %

SGLTP 2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)

Causes of antihypertensive effect:

• $\downarrow$ weight loss
• $\downarrow$ uricaemia
• $\uparrow$ natriuresis

SGLTP 2 inhibitors (sodium-glucose cotransporter-2 inhibitors)

SGLTP 2 inhibitors
(sodium-glucose cotransporter-2 inhibitors)

• Randomized placebo controlled study with „cross-over” design
• 59 diabetes mellitus type 2 patients
• 10 mg dapagliflozine vs placebo during 6 weeks
• It leads to:
  ↓ SBP by 3.0 mmHg
  ↓ DBP by 1.6 mmHg

Skin Na-MRI

Antihypertensive properties of non-classic antihypertensive drugs

1. Anti-obesity drugs

2. Drugs used in uric acid lowering therapy

3. Anti-diabetic drugs
   • Metformin
   • SGLT-2 inhibitors (sodium-glucose cotransporter-2 inhibitors)
   • GLP-1 receptor agonists (glucagon-like peptide-1)

4. Calcimimetics

5. Phosphodiesterase type 5 inhibitors
GLP-1 receptor agonists (glucagon-like peptide-1)

- Exenatide
- Liraglutide

Activation of the GLP-1 receptor by exogenous agonists

Diagram showing the effects of GLP-1 and GIP on insulin and glucagon production, as well as the role of DPP-4 in cleaving intact GLP-1 and GIP.
GLP-1 receptor agonists (glucagon-like peptide-1)

- Meta-analysis of 31 randomized placebo-controlled studies involving 4807 patients with diabetes type 2 treated with GLP-1 receptor agonists (exenatide or liraglutide)
- GLP-1 receptor agonists leads to: ↓ SBP by 1.8 mmHg
  ↓ DBP by 0.5 mmHg
- The antihypertensive effect of GLP-1 receptor agonists is observed after 2-3 weeks of treatment

GLP-1 receptor agonists (glucagon-like peptide-1)

• Causes of antihypertensive effect:
  - vascular relaxation (GLP-1 receptor activation in endothelial cells enhances NO production)
  - weight loss
Antihypertensive properties of non-classic antihypertensive drugs

1. Anti-obesity drugs
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4. Calcimimetics
5. Phosphodiesterase type 5 inhibitors
Calcimimetics
Cinacalcet

• Calcimimetics increase calcium receptor sensitivity to calcium through its allosteric modulation
• Calcimimetics reduces serum PTH concentration
• Calcimimetics are used in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease treated with haemodialysis

Calcimimetics
Cinacalcet

- 58 hemodialysis patients with CKD and secondary hyperparathyroidism
- Cinacalcet used during 6 months; mean dose: 51 mg
- Reduction of serum PTH concentration from 1138 to 772 pg/ml

Calcimimetics
Cinacalcet
EVOLVE study

Calcimimetics
Cinacalcet

Causes of antihypertensive cinacalcet effect:
• stimulation of calcium receptors in vascular endothelial cells enhancing the production of nitric oxide
• serum PTH concentration reduction

PTH has hypertensinogenic properties

- 6545 participants of *Multi-Ethnic Study of Atherosclerosis* study

<table>
<thead>
<tr>
<th>Serum PTH Category (pg/ml)</th>
<th>Hypertension</th>
<th>Systolic blood pressure, mmHg</th>
<th>Diastolic blood pressure, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32.8</td>
<td>688 (36%)</td>
<td>121.9 ±20.3</td>
<td>70.4 ±9.8</td>
</tr>
<tr>
<td>32.9 – 44.2</td>
<td>783 (41%)</td>
<td>124.8 ±20.6</td>
<td>71.4 ±10.1</td>
</tr>
<tr>
<td>44.3 – 65</td>
<td>953 (50%)</td>
<td>129.1 ±21.4</td>
<td>72.7 ±10.2</td>
</tr>
<tr>
<td>&gt;65</td>
<td>478 (62%)</td>
<td>135 ±23.4</td>
<td>74.2 ±11.4</td>
</tr>
</tbody>
</table>

PTH has hypertensinogenic properties

- Intravenous infusion of PTH leads to blood pressure increase

- In rats with normal blood pressure (WKY) and in hypertensive rats (SHR) after parathyroidectomy, decrease of blood pressure is observed

- In patients with hypertension and primary hyperparathyroidism after parathyroidectomy, decrease of blood pressure is found
  Heyliger A. et al. Surgery 2009; 146: 1042–1047

- In hemodialysis patients with CKD and secondary hyperparathyroidism after parathyroidectomy, decrease of blood pressure is observed
Antihypertensive properties of non-classic antihypertensive drugs

1. Anti-obesity drugs
2. Drugs used in uric acid lowering therapy
3. Anti-diabetic drugs
4. Calcimimetics
5. Phosphodiesterase type 5 inhibitors
Phosphodiesterase type 5 inhibitors inhibit cGMP breakdown in smooth muscle cells. Increasing cGMP cytoplasmatic concentration in smooth muscle cells leads to vascular relaxation.

- Sildenafil
- Vardenafil
- Tadalafil
Phosphodiesterase type 5 inhibitors

- Randomized placebo-controlled study with "cross-over" design
- 22 patients with hypertension without pharmacological treatment
- Sildenafil 50 mg vs placebo
- 1 hour after sildenafil dose:
  - ↓ SBP by 9 mmHg
  - ↓ DBP by 6 mmHg

Phosphodiesterase type 5 inhibitors

• Randomized placebo-controlled study, with "cross-over" design
• 6 patients with resistant hypertension
• Sildenafil 50 mg vs placebo
• 1 hour after sildenafil dose:

  ▼ SBP by 10 mmHg
  ▼ DBP by 8 mmHg

Phosphodiesterase type 5 inhibitors

• Randomized placebo-controlled study, with "cross-over" design
• 22 participants with hypertension without pharmacological treatment
• Sildenafil 3 x 50 mg daily vs placebo
• After 16 days of sildenafil treatment:
  \[
  \downarrow \text{SBP by 9 mmHg} \\
  \downarrow \text{DBP by 7 mmHg}
  \]

Antihypertensive properties of non-classic antihypertensive drugs

Drugs that are not discussed during this lecture due to inconclusive data concerning their antihypertensive effect:

- statins
- bromocriptine
- dipeptidyl peptidase Inhibitors - 4 (DPP-4)
- vitamin D
### Clinical relevance of antihypertensive properties of non-hypertensive drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>↓ SBP by 9.0 mmHg</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>↓ SBP by 6.0 mmHg</td>
</tr>
<tr>
<td>SGLTP-2 inhibitors</td>
<td>↓ SBP by 4.0 mmHg</td>
</tr>
<tr>
<td>Orlistat</td>
<td>↓ SBP by 2.5 mmHg</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>↓ SBP by 2.2 mmHg</td>
</tr>
<tr>
<td>Metformin</td>
<td>↓ SBP by 2.0 mmHg</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>↓ SBP by 2.0 mmHg</td>
</tr>
</tbody>
</table>
Clinical relevance of antihypertensive properties of non-hypertensive drugs

- Patient with diabetes type 2 and hyperuricaemia treated with: *metformin, empagliflozin* and *allopurinol*
  ↓ SBP by 12 mmHg
- Patient with hiperuricaemia and erectile dysfuntion treated with: *allopurinol* and *sildenafil*
  ↓ SBP by 15 mmHg
- Patient with diabetes type 2 and erectile dysfunction treated with: *metformin, empagliflozin* and *sildenafil*
  ↓ SBP by 15 mmHg
Clinical relevance of antihypertensive properties of non-hypertensive drugs

- Sildenafil, allopurinol, SGLT-P-2 inhibitors
  ↓ SBP by 4.0-9.0 mmHg

- Orlistat, cinacalcet, metformin, GLP-1 receptor agonists
  ↓ SBP by 2.0-2.5 mmHg

- Meta-analysis of prospective observational studies involving one million adults:
  ↓ SBP by 3-4 mmHg leads to:
  ↓ by 20% the risk of death due to stroke
  ↓ by 12% the risk of death due to ischemic heart disease

Conclusions

1. Many drugs which are non-classic antihypertensive drugs may reduce blood pressure

2. In some patients with prehypertension, the antihypertensive properties of non-hypotensive drugs might be of clinical relevance. This issue needs further clinical studies.
Thank you for your attention