Antihypertensives: ACE-Inhibitors and Sartans

The arterial hypertonia can be reduced with general measures often. However, medicinal approaches are also advisable in order to reach target blood pressures, which are in an area, as normal as possible. The most commonly prescribed drug is ACE-inhibitors, as they are cheap in price, followed by sartans. Both substances affect the renin-angiotensin-aldosterone system (RAAS) and reduce the blood pressure by the thereby conveyed effects.
Overview over ACE-inhibitors

Most ACE-inhibitors are prodrugs, which are activated by esterases in the liver after enteric resorption. The most important ones are:

- Benazepril
- Cilazapril
- Enalapril (moderate to long half-life period, so that the ingestion has to take place twice a day)
- Fosinopril
- Moexipril
- Perindopril
- Quinapril
- Ramipril (today’s cheapest antihypertensive, long half-life period)
- Spirapril
- Trandolapril

The only two ACE-inhibitors that are not prodrugs (do not need activation) are:

- Captopril (shortly active, only suitable for the initial adjustment)
- Lisinopril (long half-life period)

Effects of ACE-inhibitors

ACE-inhibitors inhibit the angiotensin-converting enzyme (ACE). So less angiotensin I is converted to angiotensin II (the active form). This leads to less angiotensin II (a powerful vasoconstrictor). So the end results are decreased vasoconstriction, afterload and blood pressure.

Furthermore, the production of aldosterone is decreased due to the decreased angiotensin II, so that less sodium and water are being reabsorbed in the kidney and diuresis takes place. This decreases total body water and edema (if present). The excretion of potassium is decreased.
The excretion of epinephrine and norepinephrine from sympathetic nerve endings and the adrenal medulla is reduced via AT1 receptors due to the decreased angiotensin II concentration. Thereby, inhibiting the sympathetic nervous system. This effect on the blood pressure reduction is controversial.

But normally ACE does not only act on angiotensin I, it is also a kinase, which inactivates bradykinin, kallidin and substance P. If ACE is inhibited, the concentrations of these peptides will rise and will promote an excretion of NO and prostacyclin out of the endothelium, which in turn act to vasodilate. This contributes to blood pressure reduction.

The increase of bradykinin in the myocardium also has a cardioprotective effect. An inhibition of growth appears to take place both in the heart and the vessels, which leads to a reduced mortality during ACE inhibitor treatment. A renal protective effect is significant during ACE inhibitor treatment, too. The efferent arterioles of the kidneys are vasodilated and glomerular filtration rate is decreased – reducing pressure in the glomeruli.

**Adverse effects of ACE inhibitors**

The most important adverse effects of ACE inhibitors are a dry cough (probably due to the increase of substance P), which in many cases leads to a discontinuation of treatment, angioedema, and hyperkalemia. Hyperkalemia occurs most often when ACE inhibitors are used in combination with aldosterone receptor antagonists or potassium-sparing diuretics, as well as in patients with renal insufficiency or diabetes mellitus.

Initial dosage should be titrated up in order to avoid excessive blood pressure reduction (hypotension). Other possible adverse effects are nausea and headache as well as (allergic) exanthemata. An increase of creatinine can occur, which is not problematic when increased by up to 30%, but should create suspicion of renal artery stenosis if the level is higher.

**Indications for the use of ACE-inhibitors**

ACE inhibitors are used for the treatment of the primary arterial hypertension and are a method of the first choice with accompanying heart failure and renal insufficiency. The prescription of ACE inhibitors is also indicated after a myocardial infarction (second till
ACE inhibitors are prescribed often with accompanying diabetes mellitus or a metabolic syndrome as they are said to be metabolically neutral.

Contraindications of ACE inhibitors

The most important contraindications for the use of ACE inhibitors are renal artery stenosis or a severe renal insufficiency (with creatinine > 3mg/dl). Other contraindications are aortic stenosis and pregnancy.

Dosage recommendations for ACE inhibitors

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect duration (in hours)</th>
<th>Mean antihypertensive dosage (in mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>8-12</td>
<td>2-3 x 12,5-50</td>
</tr>
<tr>
<td>Ramipril</td>
<td>24-48</td>
<td>1 x 2,5-5</td>
</tr>
<tr>
<td>Enalapril</td>
<td>12-24</td>
<td>1-2 x 5-10</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>24</td>
<td>1 x 10-20</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>24</td>
<td>1 x 5-10</td>
</tr>
<tr>
<td>Quinapril</td>
<td>12-24</td>
<td>1-2 x 10</td>
</tr>
</tbody>
</table>

Angiotensin II Receptor Blockers (ATII Blockers)

Overview

Angiotensin II receptor antagonists or blockers create effects similar to ACE inhibitors, but they are not the first treatment of choice due to high costs. The most important ones are:

- Losartan
- Valsartan
- Candesartan
- Eprosartan
- Irbesartan
- Olmesartan
- Telmisartan

Mechanism of action and effect of ATII blockers

The effects of ATII blockers resemble those of ACE inhibitors, as they also prevent the effects caused by angiotensin II, but instead of inhibiting production of ATII (ACE inhibitors), they inhibit binding of ATII to their receptors. This also results in vasodilatation, decreased aldosterone productions, reduced sodium and water reabsorption and diuresis.

Like ACE inhibitors, blood pressure is reduced and cardiac insufficiency can be improved. There is also a renal protective effect. Unlike ACE inhibitors, the effects on the bradykinin metabolism are absent because ACE is still active with ATII blocker therapy.

Adverse effects of ATII blockers

The adverse effects are similar to those of ACE inhibitors, especially
the hyperkalemia. The angioedema occurs less than during ACE inhibitor treatment. Another advantage to ACE inhibitors is the reduced appearance of a dry cough.

Indications for the use of Angiotensin II blockers

Angiotensin II blockers help, just like ACE inhibitors, for the treatment of arterial hypertension. They can also be used for chronic cardiac insufficiency. Angiotensin II blockers are normally used in patients that are intolerant to ACE inhibitors (usual patients with a cough due to ACE inhibitor use).

Contraindications of Angiotensin II blockers

The contraindications for the treatment with Angiotensin II blockers, they include renal artery stenosis, renal insufficiency, aortic stenosis, and pregnancy.

Dosage for Angiotensin II blockers

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect duration (in hours)</th>
<th>Mean antihypertensive dosage (in mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan cilexetil</td>
<td>≈ 24</td>
<td>1 x 4-16</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>≈ 24</td>
<td>1 x 150-300</td>
</tr>
<tr>
<td>Losartan</td>
<td>&lt; 24</td>
<td>1-2 x 50</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>≈ 24</td>
<td>1 x 10-20</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>&gt; 24</td>
<td>1 x 20-80</td>
</tr>
<tr>
<td>Valsartan</td>
<td>≈ 24</td>
<td>1 x 80-160</td>
</tr>
</tbody>
</table>

Review Questions

The correct answers can be found below the references.

1. A patient complains to his physician about a dry cough, which he is not able to get rid of since his last hospital stay. Which substance is most considerably for this?
   A. Clopidogrel
   B. Acetylsalicylic acid
   C. Ramipril
   D. Simvastatin
   E. Pantoprazole

2. Which of the following medicaments should not be used in case of ambilateral renal artery stenosis?
   A. Carvedilol
   B. Reserpine
   C. Chlortalidone
   D. Losartan
   E. Nitrendipine

3. Which of the following substances works directly and does not need to be activated first?
   A. Perindopril
   B. Captopril
C. Quinapril
D. Ramipril
E. Spirapril

References


**Correct answers:** 1C, 2D, 3B

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