Clinical pharmacology of diuretics in the international system of ATC (anatomic-therapeutic-chemical) is presented. Classification of this group by the action mechanism and caused effects is provided. Pharmacokinetics and pharmacodynamics features, indications and principles of diuretics usage in clinics are considered. Contraindications, side effects and interaction with other drugs of this group are discussed in detail.

KEY WORDS: clinical pharmacology, diuretics

INTRODUCTION


As far back in the XVI century it was clear that organic mercury compounds have diuretic characteristics but as diuretics they have been used in medicine since 1920 in Vienna. The next stage in diuretics creation was based on the results of acidosis development observation in patients, who got sulfanilamides, which is not typical for modern sulfanilamide remedies. Acidosis was clarified to be stipulated for carbonic anhydrase enzyme inhibition in kidneys [5]. Further studies caused the creation of powerful inhibitor of acetazolamide carbonic anhydrase in 1951 [6]. In 1957 in the process of preparations chemically close to
acetazolamide study chlorothiazide was obtained, which weakly inhibited carbonic anhydrase, that is why this property could not explain their diuretic efficacy [7]. Both acetazolamide and thiazide structurally are close to sulfanilamides. Their structure modification caused the creation of more effective diuretics, such as furosemide, etacryn acid, bumetanide as well as potassium preserving diuretics such as triamteren and amiloride, etc. [8].

CLASSIFICATION OF DIURETICS

ATC classification

C: MEDICATIONS, EFFECTING CARDIO-VASCULAR SYSTEM
C03 Diuretics
C03A Diuretics with moderately expressed activity, thiazides group
C03AA Simple thiazide diuretics
C03AA03 Hydrochlorothiazide
C03B Nonthiazide diuretics with moderately expressed activity
C03BA Sulfanilamides, simple preparations
C03BA03 Clopamide
C03BA04 Chlorthalidone
C03BA11 Indapamide
C03BX Other nonthiazide diuretics with moderately expressed effect
C03BX10 Herbal preparations with diuretic effect
C03C Highly active diuretics
C03CA Simple sulfamides preparations
C03CA01 Furosemide
C03CA02 Bumetanide
C03CA04 Thorasemide
C03C3 Derivatives of aryloxyazinyl acid
C03CC01 Etacrin acid
C03D Potassium preserving diuretics
C03DA Aldosterone antagonists
C03DA01 Spironolactone

Classification depending on the scene of action in nephron

Classification of diuretics depending on their scene of action in nephron is widely disseminated in clinical practice:
1) on proximal part of straight tubule –
a) Carbonic anhydrase inhibitors (acetazolamide).
   b) Osmotic diuretics (mannitol, urea).
2) on ascending area of Genle loop – «loop» diuretics (furosemide, etacryn acid, etc.);
3) on distal part of straight tubule – thiazide and thiazide-like diuretics (hydrochlorothiazide, chlorthalidone, indapamide, etc.);
4) in general in the area of collective and distal tubules (potassium preserving diuretics);
5) onglomerule (aminophylline, teobromine).

Classification depending on natriuretic effect

Diuretics are divided into the groups depending on natriuretic effect, expressed in percentage of excelling sodium from general amount of sodium, filtered in renal tubules:

1) strong organic compounds of mercury (mersalile, at present it is not used in clinical practice):
   – derivatives of sulfamylontranile acid (furosemide, bumetanid);
   – derivatives of phenoxy-acetic acid (etacrin acid, indacrinon).

2) With moderately expressed natriuretic effect (causing excretion of 5-10 % sodium, filtered):
   – derivatives of bensotiathiazine (thiazides and hydrothiazides).
   – heterocyclic combinations similar in mechanism of tubule activity to thiazide diuretics (chlorthalione, clopamide, indapamide).

3) weak (causing excretion of less than 5 % filtered sodium):
   – potassium preserving;
   – carbonic anhydrase inhibitors;
   – osmotic diuretics.

PHARMACOKINETICS

Main pharmacokinetic indicators of diuretics are presented in table 1.

Loop diuretics nearly completely absorb from gastrointestinal tract, though absorption individual indices vary greatly. They relatively quickly metabolize in liver.

Thiazides and thiazide-like diuretics have high bioavailability under intake. Due to sufficient lipophilicity and moderately expressed link with proteins they deeply penetrate into organs and tissues. Hydrochlorothiazide and chlorthalidone poorly metabolize in liver and is nearly absolutely excreted by kidneys unchanged. Indapamide practically completely metabolize in liver and only a tiny part of active remedy is excreted by kidneys.

Carbonic anhydrase inhibitors are practically completely absorbed from gastrointestinal
tract. In 95% of cases they are linked with protein in blood plasma. They are not metabolized in organism and are completely excreted by kidneys unchanged.

Table 1

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Bioavailability (%)</th>
<th>T₁/₂ (h)</th>
<th>Main way of elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide diuretics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>60-80</td>
<td>10-12 (2,5)</td>
<td>Kidneys</td>
</tr>
<tr>
<td>Indapamide</td>
<td>90-100</td>
<td>15-25</td>
<td>Kidneys + liver (30%)</td>
</tr>
<tr>
<td>Clopamide</td>
<td>?</td>
<td>4-6</td>
<td>Kidneys</td>
</tr>
<tr>
<td>Xipamide</td>
<td>70-90</td>
<td>5-7 (14)</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Metolazone</td>
<td>50-60</td>
<td>8-14</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>60-65</td>
<td>24-50</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Chlorthiazide</td>
<td>33-65</td>
<td>15-27 (1,5)</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td><strong>Loop diuretics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>60-90</td>
<td>0,3-1,5</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Pyretanide</td>
<td>80-90</td>
<td>0,6-1,5</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Torasemide</td>
<td>80-90</td>
<td>0,8-6,0</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10-90</td>
<td>0,3-3,4</td>
<td>Kidneys + liver (40%)</td>
</tr>
<tr>
<td>Etacrin acid</td>
<td>30-35</td>
<td>12</td>
<td>Kidneys + liver</td>
</tr>
<tr>
<td><strong>Potassium preserving diuretics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>50</td>
<td>6-9 (18-22)</td>
<td>Kidneys + liver (50%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>60-90</td>
<td>14 (1,5)</td>
<td>Kidneys + liver (20%)</td>
</tr>
<tr>
<td>Triamteren</td>
<td>50</td>
<td>3-5</td>
<td>Kidneys + liver</td>
</tr>
</tbody>
</table>

Note: T₁/₂ – semi-ejection period; in brackets – other meanings of T₁/₂, if they rapidly differ from the given/
reserves and vascular effects regardless natriuresis amount. Antianginal effect of diuretics is stipulated for intracellular calcium decrease with magnesium content preservation, decrease of vascular wall stiffness and promote of effective cardiomyocytes relaxation into diastole. In this case prostacyclin synthesis increases, thrombocytes aggregation and thromboxane A2 ejection decreases, totally exerts positive hemodynamic effect on account of loading decrease on left ventricle. Diuretics improve microcirculation in kidneys, eliminate microalbuminuria which is the marker of generalized vascular affection and a predictor of cardio-vascular and renal complications.

Antithrombotic effect of diuretics (indapamide) is stipulated for decrease of low density atherogenic cholesterol and triglycerides level with simultaneous increase of high density lipoprotein concentration.

Dehydration effect of diuretics (mannit, urea) is stipulated for increase of osmotic pressure in tubules and water reabsorption obstruction. They are filtered by kidneys without further tubular reabsorption which causes water retention in tubules and increase of urine volume. Simultaneously natriuresis increases considerably without potassiumuresis sufficient increase. They cause decrease of circulating liquid volume (in connection with osmotic pressure growth in bloodstream), decrease of intracranial and intraocular pressure. Oppression of carbonanhydrase causes decrease of intraocular pressure, inhibition of excessive paroxysmal neurons discharges and antiepileptic activity.

Antiepileptic effect (acetozolamide) is stipulated for random suppression of carbonanhydrase (enzyme, catalyzing reverse reaction of carbon dioxide hydration and further carbonic acid dissociation).

According to LIVE trial (Left ventricular hypertrophy: Indapamide Versus Enalapril) on the background of long term indapamide therapy - 1,5 mg per day - reliable decrease of mass index of left ventricle was observed versus enalapril therapy (20 mg per day).

According to most experimental and clinical studied diuretics have no sufficient nephroprotective activity. On the contrary, their monotherapy can accelerate renal function decrease in spite of antihypertensive effect. Though the results of early trial HYVET (Hypertension in the Very Elderly Trial) in elderly patients demonstrated that indapamide produced nephroprotective activity.

Diuretics provide bronchodilatory and spasmolytic effects (aminophylline and theobromine) on the account of bronchial smooth muscles, periphery arteries, gastrointestinal smooth muscles, biliary tract relaxation. They also increase contractility of skeleton muscles (including respiratory).

**INDICATIONS AND USAGE PRINCIPLES**

Main indications to diuretics clinical use are:
- arterial hypertension (AH): isolated systole AH in elderly persons;
- edematous syndrome, cause by Na delay: chronic heart failure (CHF), chronic renal failure (CRF), nephritic syndrome, edemas and ascites under hepatocirrhosis;
- osteoporosis, hypercalcemia (thiazides);
- (primary) open angle glaucoma, secondary glaucoma, pre-operative decrease of intraocular pressure (carbonic anhydrase inhibitors);
- pseudohyperaldosteronism – Liddle syndrome (potassium preserving diuretics);
- primary and secondary hyperaldosteronism (spironolactone);
- hyperuricemia (spironolactone).

Daily doses and reception frequency of diuretics are presented in tab. 2.

**SIDE EFFECTS**

Most side effects of diuretics are connected with electrolytic and water balance changes, urine pH shift into alkaline side and metabolic acidosis development. Such side effects are:
- Electrolytic: intracellular liquid reserves depletion, arterial hypotension, hypocalcaemia (thiazides), hyperkalemia (aldosterone antagonists, potassium preserving diuretics), nypochloremia, nephrocalcinosis, metabolic alkalosis, hypomagnesaemia, hypocalcaemia, hyperuricemia.
- Central nervous system (CNS) disorders: dizziness, headache, weakness, parasthesias.
- Gastrointestinal: anorexia, nausea, vomiting, colic, diarrhea, constipation, cholecystitis, pancreatitis.
- Sexual: impotence, libido decrease.
- Hematologic (blood dyscrasia): thrombocytopenia, agranulocytosis, thrombocytopenia purpura.
- Dermatologic: skin rash, photosensibilization.
Other: hyperglycemia, increase of general cholesterol level in blood, triglycerides level increase, low density lipoproteins level increase.

Table 2

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Average doses (mg/day)</th>
<th>Reception frequency</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12,5-50</td>
<td>1</td>
<td>Most efficient for AH treatment than loop diuretics excluding the patients with creatinine more than 177 mcmole/l</td>
</tr>
<tr>
<td><strong>Thiazide-like diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12,5-25</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Indapamide-retard</td>
<td>1,5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torasemide</td>
<td>2,5-10</td>
<td>1-2</td>
<td>The use of big doses is possible in treatment of patients with CRF and CHF.</td>
</tr>
<tr>
<td>Forisemide</td>
<td>20-80</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td><strong>Potassium preserving diuretics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>5-10</td>
<td>1-2</td>
<td>Is not used if creatinine is more than 220 mcmole/l</td>
</tr>
<tr>
<td>Tiamteren</td>
<td>50-100</td>
<td>1-2</td>
<td></td>
</tr>
<tr>
<td><strong>Aldosteron antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25-50</td>
<td>2-3</td>
<td>Is not used if creatinine is more than 220 mcmole/l</td>
</tr>
</tbody>
</table>

**CONTRAINDICATIONS**

Hypokalemia, gout, asymptomatic hyperuricemia, decompensated hepatocirrhosis, sulpha-nilamide derivatives intolerance (hypo-glycemic and antibacterial preparations), severe respiratory failure, acute renal failure. In high doses thiazide diuretics are contrain-dicated under sugar diabetes, especially of the 1st type. Diuretics should be prescribed with great care to the patients with ventricular arrhythmias or to those who get heart glycosides or lithium salts.

**INTERCONNECTION OF DIURETICS WITH OTHER REMEDIES**

Loop diuretics are able to interact pharmacodynamically and pharmacokinetically with many preparations.

They reinforce the activity of anticoagulants, hypotensive remedies, semipolarizing myorelaxants; raise the side effects development risk of aminoglycosides, heart glycosides and diuretics, excreting potassium and GCS; raise propranolol and lithium concentration in blood plasma; lower oral hypolipidemic remedies effects. Diuretics activity can decrease under simultaneous application together with indomethacin and other non-steroid anti-inflammatory drugs (NSAIDs).

Thiazide and thiazide-like diuretics lower the efficacy of antigout remedies, sulphonylurea preparations, insulin. They can reinforce the activity of anesthetics, diaoxide, heart glycosides, lithium preparations and loop diuretics. Such remedies as NSAIDs and cholestyramine lower the efficacy of diuretics therapy, thus amphotericin B and corticosteroids can reinforce hypokalemic effect of thiazide and thiazide-like diuretics.

Carbonic anhydrase inhibitors interact with lithium preparations which cause lowering of diuretics effect.

Spironolactone can raise digoxin concentration in blood plasma and increase the risk of side effects development, including arrhythmia. Combined application of remedies with ACE inhibitors, indomethacin and other potassium preserving
diuretics can cause the development of hyperkalemia (especially on the background of renal failure). NSAIDs, lowering glomerular filtration and diuresis weaken diuretic activity of spironolactone.

REFERENCES