**Lesson 2**

**Analysis of drugs containing isoquinoline derivatives: pharmaceutical forms of papaverine hydrochloride, glaucine hydrochloride and drotaverine hydrochloride (No-shpa).**

**Isoquinoline derivatives**

Isoquinoline differs from quinoline by the location of the nitrogen atom in the molecule:



Isoquinoline and its derivatives are included in the molecule of many alkaloids. The preparations of this group of alkaloids used in medicine are isoquinoline, 1-benzylzioquinoline (papeverine, drotaverine), morphinan (morphine, codeine, ethylmorphine, naltrexone) and aporphine (apomorphine, glaucine) derivatives:



Morphine and amorphine are condensed complex heterocyclic systems. Their molecule includes a partially hydrogenated aromatic phenethrene nucleus. Some rings of the phenanthrene core are part of tetrahydroisoquinoline.

Reed is used as a source of raw materials in the production of alkaloids derived from 1-benzylisoquinoline, aporphine and morphinan (phenanthrenisoquinoline). Opium consists of the milky juice obtained from the aerial part or cones of the poppy plant (Papaver somniferum L.). Opium contains up to 25 alkaloids, including morphine, narcotine, papaverine, codeine, thebaine, etc. , as well as sugars, proteins, resinous substances, mineral salts, etc. there is Alkaloids contained in opium are used in medical practice as medicines or in the preparation of semi-synthetic analogues. Alkaloids make up about 25% of the total weight of teak, they are in the form of mecon (β-oxy-γ-pyrone-α,α1 – dicarbon), salts of lactic and sulfuric acids (meconates, lactates and sulfates):

lactates and sulfates) are in the form of:



meconic acid lactic acid

To get alkaloids from opium, it is treated with hot water (50-55 oC), the salts of alkaloids pass into the water. Then they concentrate the aqueous extract and separate the alkaloids into individual substances. For this purpose, different alkaloids have different degrees of basicity or solubility in organic solvents in basic form, etc. they use their properties.

Physico-chemical methods such as chromatography and electrophoresis are used to extract and separate alkaloids.

In addition to natural alkaloids, their semi-synthetic counterparts are also used in medicine.

Benzylisoquinoline derivatives

The main representative of this group is papaverine alkaloid. Papaverine was first obtained from opium in 1884 and synthesized in 1910.

Papaverine-hydrochloride and its semi-synthetic analogue, drotaverine-hydrochloride, are used in medical practice.

**Papaverine Hydrochloride – Papaverine Hydrochloride**

O

C

H

3

7

6

8

1

2

3

4

5

O

3

H

C

N

O

3

H

C

C

H

2

O

3

H

C

5

4

6

3

1

2

R

R

1

v

ə

y

a

C

2

0

H

2

1

N

O

4

H

C

l

.

$∙$HCl

**6,7-Dimethoxy-1-(3/,4/-dimethoxybenzyl)-**

**-isoquinoline hydrochloride**

**M.k. 375,86**

Papaverine was first obtained from opium. Opium contains up to 0.4-1.5% papaverine (the dried milky juice obtained from the unripe cones of Papaver somniferum).

Papaverine, which is used for medical purposes, is obtained by synthesis (as a result of the interaction of 3,4-dimethoxybenzaldehyde and hippuric acid) and processed in the form of a hydrochloride salt. It is also possible to buy the drug by another method: the corresponding amide (III) is obtained from 3,4-dimethoxyphenylethylamine (I) and chloroanhydride (II) of 3,4-dimethoxy-phenylacetic acid; then 3,4-dihydropapaverine (IV) is obtained as a result of dehydration, and papaverine-base (V) is obtained from its dehydrogenation. When papaverine reacts with an alcoholic solution of the base with hydrogen chloride, papaverine hydrochloride is obtained:

N

H

2

O

3

H

C

O

3

H

C

+

O

3

H

C

C

H

2

C

O

C

l

O

C

H

3

-

H

C

l

I

I

I

I

I

I

N

H

2

O

3

H

C

O

3

H

C

C

O

C

H

2

O

3

H

C

O

3

H

C

-

H

2

O

I

V

N

O

3

H

C

O

3

H

C

-

2

H

O

3

H

C

C

H

2

O

3

H

C

V

N

O

3

H

C

O

3

H

C

O

3

H

C

O

3

H

C

C

H

2

H

C

l

P

a

p

a

v

e

r

i

n

h

i

d

r

o

x

l

o

r

i

d

Papaverine is a weak base, its salts are easily hydrolyzed. It is a white crystalline powder, odorless and has a slightly bitter taste. It dissolves gradually in water for 40 h, in 95% alcohol, in chloroform, practically insoluble in ether.

Determination of identity

The chemical reactions used to determine the identity of benzylisoquinoline derivatives are based on substitution with halogens, the formation of various colored products as a result of oxidation, and also acid-base properties.

1) Special reagents related to alkaloids are used to determine the identity of the preparation. 0.05 g of the drug is placed in a porcelain bowl and soaked with 2 drops of nitric acid; a yellow color is obtained, and when heated on a water bath, the color changes to orange.

2) 1 ml of solid sulfuric acid is added to 0.1 g of the preparation and heated; a purple color (halochromic compound) is formed.

C

H

2

R

1

R

[

O

]

C

R

1

H

S

O

4

R

O

H

.

+

3) Papaverine-base is precipitated from the drug solution in water with sodium-acetate solution, dried and the melting temperature is determined. Papaverine-base should melt at a temperature of 145-1470C.

4) Chlorides are determined in the filtrate remaining from the 3rd determination.

5) Papaverine hydrochloride gives a colored product with Marqui's reagent (CH2O + H2SO4). When bromine water and NH3 solution are added to that solution, a purple precipitate is obtained, and when alcohol is added, a red-purple color - methylene-bispapaverine sulfate is obtained. Using this reaction, they determine the amount of papaverine photometrically.

O

3

H

C

O

3

H

C

N

H

+

O

C

H

3

O

C

H

3

+

O

C

H

3

N

H

O

C

H

3

O

C

H

3

O

C

H

3

S

O

4

2

-

**methylenebispapaverine-sulfate**

6) Papaverine hydrochloride precipitates with many precipitating reagents (Dragendorf-(KBiI4), Mayer (K2HgI4), Marme (K2CdI4), etc.).

With bromine water, a yellow precipitate-brompapaverine-hydrobromide (C20H20O4NBr ∙ HBr), with a solution of iodine in alcohol, dark-red crystals-diodopapaverine-hydroiodide (C20H19O4N ∙ I2 ∙ HI), with picric acid, a yellow precipitate-picrate (melting temperature 2200C) is formed.

7) Caroline's test. Solid sulfuric acid and acetic anhydride are added to the crystals of the preparation and heated, a yellow color with green fluorescence is obtained. A similar reaction occurs with Frede's reagent (solid sulfuric and nitric acids).

8) Solid H2SO4 and FeCl3 gives a green color. When HNO3 is added, the color changes to red-brown.

9) IR-spectroscopy: the IR-spectrum of papaverine hydrochloride taken in the fields of 4000-400 cm-1 should be the same as the IR-spectrum of the standard sample.

10) UV-spectrophotometry: the solution of the drug in 0.01 M hydrochloric acid gives maximum absorption at 251, 285 and 309 nm d.u.

Quantification

1) Aqueous titration method. The preparation etc. dissolved in a mixture of glacial acetic acid and mercury 2-acetate and titrated with 0.1 M HClO4 (indicator violet crystal; T=0.03759 g/ml). In parallel, a control experiment is performed (see morphine-hydrochloride).

2) Neutralization (alkalimetry) method. The preparation etc. dissolve in 5 ml alcohol and water mixture neutralized by phenolphthalein and titrate with 0.02 M NaOH solution until pink color (indicator - phenolphthalein; T=0.0075 g/ml).

3) Spectrophotometry method. The optical density of the 2% injection solution of the drug is measured at a wavelength of 309 nm.

In parallel, the optical density of the standard solution is determined.

Papaverine is an antispasmodic substance. It is used in hypertension, spasm of cerebral vessels, angina pectoris, and spasm of muscular internal organs. It is a component of drugs called Papazol, Nikoverin, Andipal, Teodibaverin.

Intracavernosal drug Papaverine is injected into the porous part of the male gonads to stimulate erection during impotence in men. 0.01 and 0.04 g tablets, 2 ml of 2% solution for injection, 0.2 g suppositories are released.

Papaverine-hydrochloride turns yellow due to exposure to light and oxygen during storage. This is due to the formation of papaverinol and papaveraldine, which are oxidation products.

The drug is stored in tightly closed containers, protected from light.

**Drotaverine Hydrochloride - Drotaverine Hydrochloride**

**(No-spa – No-spa)**

C

H

O

5

H

2

C

O

5

H

2

C

O

5

H

2

C

O

5

H

2

C

N

H

H

C

l

.

**1-(3,4-Diethoxybenzylidene 6,7-diethoxy-1,2,3,4-**

**-tetrahydroisoquinoline hydrochloride)**

**M.k. 434**

It is a pale yellow odorless crystalline powder. Soluble in water and alcohol. Melting point is 208-211℃.

Determination of identity

1) UV-spectrophotometry: a 0.001% solution of the drug in 0.1 M hydrochloric acid gives maximum absorption in the spectrophotometer at wavelengths of 241±1, 302±2 and 353±2 nm.

2) The solution of the preparation with solid H2SO4 is yellow in color. When 1 drop of 2 M HNO3 is added to it, the solution turns brown.

3) A reaction related to chlorides is carried out.

4) Solutions of the preparation and papaverine in an acidic environment give blue fluorescence under the influence of KMnO4.

Quantification

1) Argentometry (Folgard) method (T=0.0434 g/ml). Place 5 ml (d.h.) 2% solution of the drug in a 100 ml flask, add 20 ml of ethyl alcohol and acidify the solution with HNO3. Then 10 ml of 0.1 M silver-nitrate solution is added, and its excess is titrated with 0.1 M ammonium rhodanide (indicator-iron ammonium salt). In parallel, a control experiment is carried out. The amount of No-span in 1 ml of the preparation should be 0.019-0.021 g.

2) Neutralization (alkalimetry) method. The preparation etc. titrate with 0.1 M NaOH solution in the presence of water-alcohol or water-chloroform (indicator phenolphthalein).

3) Spectrophotometry method. The optical density of the drug and standard drotaverine hydrochloride solution in 0.1 M hydrochloric acid is measured at a wavelength of 353 nm.

4) Complex sonometry method. The preparation etc. It is precipitated with Marme reagent (K2CdI4) (Composition of Marme reagent: 1 g CdI2+ 6 g KI + distilled water until reaching 100 ml).

After a certain part of the solution is filtered, the excess of the reagent is determined by titration with 0.01 M Trilon B. In parallel, a control experiment is performed (indicator-acidic chrome dark blue (T=0.00868 g/ml).

It has a stronger and longer lasting spasmolytic effect than papaverine. It is used in spasm of the stomach and intestines, constipation, diseases of the biliary and urinary tracts, stomach and duodenal ulcers, spasm of peripheral vessels. The drug is available in 0.04 g tablets, 2% solution for injection in the amount of 2 ml. No-shpa is included in the combined preparations called Nicospanum.

The drug is stored in tightly closed containers, protected from light.

APORPHINE DERIVATIVES

Apoprofin-hydrochloride and glaucine-hydrochloride are used in medical practice from aprofin derivatives.

**Glaucine Hydrochloride (Hydrobromide)**

 **Glaucine Hydrochloride (Hydrobromide)**

C

H

3

N

.

O

3

H

C

1

2

3

4

5

6

7

8

9

1

0

H

C

l

(

H

B

r

)

O

C

H

3

O

3

H

C

O

3

H

C

**M.k. 391.9**

**4,5,7,8-tetramethoxyporphine hydrochloride**

The hydrobromide salt of glaucine is released under the name of Glauvent, and more recently also the phosphate salt.

Glaucin is obtained from the aerial part of the yellow horn tulip plant, Glaucium flavum Grantz, from the Papaveraceae-poppy family.

Glaucine hydrochloride is a white or pale yellowish, pomegranate powder. Gradually dissolving in water, it forms a cloudy solution. Hardly soluble in ethanol, soluble in chloroform.

Determination of identity

1) 0.2 g of pomegranate crushed tablet powder is mixed with 20 ml of water for 5 minutes and filtered. 5-6 drops of Marqui's reagent are added to 2 ml of filtrate; a dark red color is formed.

2) On 5 ml of that filtrate, they conduct a reaction specific to chlorides or bromides.

3) It gives an orange-red precipitate with Dragendorf's reagent, and a white precipitate with Mayer's and Marme's reagents.

4) Melting temperature is 115-1190C.

5) UV-spectrophotometry: the solution of the drug in water gives the maximum absorption at a wavelength of 300 nm.

Quantification

1) Aqueous titration method. 3 tablets are made into pomegranate powder and extracted several times with chloroform. The chloroform extracts are combined and the chloroform is evaporated. The residue is dissolved in a mixture of glacial acetic acid and mercury 2-acetate and titrated with 0.1 M HClO4 until green (indicator-purple crystal; T=0.03919 g/ml).

2) Complexonometry method. An indirect assignment is made here. Glaucin is precipitated with Marme's reagent (1 g of CdI2 and 6 g of KI in 100 ml of solution), the excess of the reagent is titrated with 0.01 M Trilon B solution (indicator - acid chromium dark blue). The determination is completed by titrating from red to blue violet in the presence of ammonia buffer solution (T=0.00784 g/ml).

It has an antitussive effect. Glaucin is released in tablets of 0.05 g, and Glauvent in tablets of 0.04 g. The composition of Broncholytin (Broncholytin) syrup consists of 0.125 g of glaucine hydrochloride, 0.1 g of ephedrine, 0.125 g of sage oil and citric acid. The weight of the syrup is 125 g.

Glaucin preparations are stored protected from light.