INSTRUCTION

On the drug medical use

Metronidazole

Solution for intravenous infusion

REGISTRATION NUMBER:_____

COMMERCIAL TITLE: Metronidazole

INTERNATIONAL NONPROPRIETARY NAME: Metronidazole

DOSAGE FORM: Solution for intravenous infusion 0.5%

COMPOSITION: Active ingredient: metronidazole – 5,0 g; inactive ingredients: sodium chloride – 7,9 g, sodium phosphate monobasic $2H_2O$ - 0,355 g, sodium phosphate dibasic - 0,162 g, citric acid - 0,229 g, water for injection - up to 1L.

DESCRIPTION: Clear, colorless or yellowish - greenish solution.

PHARMACOTHERAPEUTICAL GROUP – Antiprotozoal agent with an antimicrobial activity, nitroimidazole.

CODE ATC: J01XD01

PHARMACOLOGICAL EFFECT

Pharmacodynamics

Antiprotozoal and antimicrobial drug, 5-nitroimidazole derivative. The mechanism of action is biochemical reduction of 5-nitro group by intracellular transport proteins of anaerobic microorganisms and protozoa. Recovered 5-nitro group interacts with DNA of microbial cells by inhibiting synthesis of nucleic acids, which leads to the death of the bacteria.

The drug is *active against*: Trichomonas vaginalis, Entamoeba histolytica, Gardnerella vaginalis, Giardia intestinalis, Lamblia spp.; *anaerobic bacteria:* Bacteroides spp. (Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus), Fusobacterium spp., Veillonella spp., Prevotella spp. (Prevotella bivia, Prevotella buccae, Prevotella disiens), Eubacterium spp., Clostridium spp., Peptococcus spp., Peptostreptococcus spp. MIC for these strains is 0,125-6,25 μg/ml. In combination with amoxicillin is active against Helicobacter pylori (amoxicillin inhibits the development of resistance to metronidazole).

To the drug are resistant aerobic and facultative anaerobic microorganisms, but in the presence of mixed flora (aerobic and anaerobic) metronidazole acts synergistically with antibiotics, effective against aerobes.

The drug increases the sensitivity of tumors to radiation, has disulfiram-like effect, stimulates reparative processes.

Pharmacokinetics

Absorption

After i.v. administration at dose of 500 mg within 20 minutes, the C_{max} in serum in 1 hour is 35.2 μg/ml, in 4 hours - 33.9 μg/ml, in 8 hours - 25.7 μg/ml; C_{min} for the subsequent administration - 18 μg/ml.

At i.v. administration the C_{max} achieves within 30-60 minutes, therapeutic concentration maintains for 6-8 hours.

In normal biligenesis the concentration of metronidazole in the bile after i.v. administration can greatly exceed the concentration in plasma.

Distribution

Binding to plasma proteins - 10%. V_d in adults is 1.1 ± 0.4 L/kg, in neonates - 0.54 - 0.81 L/kg.

Metronidazole has a high penetrating power. Reaches bactericidal concentration in the lungs, kidneys, liver, brain, skin, cerebrospinal fluid, bile, saliva, amniotic fluid, abscess cavity, vaginal secretions, semen, breast milk. Penetrates into the hematoencephalic barrier, passes through the placental barrier.

Metabolism

Metabolizes (approximately 30-60%) by hydroxylation, oxidation and glucuronidation. The main metabolite - 2 oximetronidazole has antiprotozoal and antimicrobial action.

Elimination

Excretes by the kidneys (60-80%), 20% - unchanged; by the intestine - 6-15%. $T_{1/2}$ - 8 hours (6-12 hours). Renal clearance - 10.2 ml/min.

INDICATIONS FOR USE

Treatment of the infections caused by drug sensitive anaerobic microorganisms:

- abdominal infections (peritonitis, abdominal abscess, pelvic abscess, liver abscess);
- gynecological infections (endometritis, puerperal sepsis, parametritis, abscess of the fallopian tubes and ovaries, infection of vaginal fornix after surgery);
- septicemia, bacteremia, bacterial endocarditis;
- infections of the skin and soft tissues;
- bone and joint infections, osteomyelitis;
- CNS infections (meningitis, brain abscess);
- infections of the lower respiratory tract (necrotizing pneumonia, empyema, lung abscess);
- infection of the surgical wound;
- prevention of anaerobic infections in surgical interventions (mainly on abdominal and pelvic organs).

CONTRAINDICATIONS

- Leukopenia (including in anamnesis);
- Organic CNS injuries;
- Epilepsy;
- Hepatic failure (when using the drug in high doses);
- Pregnancy (I trimester);
- Breastfeeding;

- Hypersensitivity to metronidazole or other nitroimidazole derivatives, and to the other components of the preparation.

DOSAGE AND ADMINISTRATION

The drug is administered at an infusion rate of 5 ml/min.

Adults and children over the age of 12 years: the drug is administered by i.v. infusion of 500 mg every 8 hours. The course of treatment - 7 days. In case of needing the i.v.administration is continued for a longer time. The maximum daily dose – 4 g. According to indications to transfer into supporting oral administration by the dose of 400 mg, 3 times per day.

Children under the age of 12 years: i.v. infusion, slowly:

Children aged from 2 months to 12 years - 20-30 mg/kg per day as a single administration or 7.5 mg/kg every 8 hours. Depending on the severity of state the daily dose may be increased to 40 mg/kg. The course of treatment usually is 7 days.

Children under the age of 2 months - 15 mg/kg per day in a single administration or 7.5 mg/kg every 12 hours.

Using the drug in premature neonates under the age of 7 days can be observed drug accumulation. Requires monitoring the concentration of metronidazole in the plasma within a few days after initiation of therapy.

Prophylactic purposes:

Adults and children over the age of 12 years: i.v. infusion of 500 mg before surgery, on the day of surgery and the next day - 1.5 g/day (500 mg every 8 hours). In 1-2 days to transfer into supporting therapy by oral administration.

Children under the age of 12 years: 20-30 mg/kg once before 1-2 hours of surgery.

Premature neonates: 10 mg/kg once before surgery.

For patients with chronic renal failure and creatinine clearance less than 30 ml/min the maximum daily dose is 1 g.

SIDE EFFECTS

Digestive system: nausea, vomiting, diarrhea, intestinal colic, constipation, metallic taste in the mouth, dry mouth, glossitis, stomatitis, pancreatitis.

Hepatobiliary system: very rarely - increased activity of liver enzymes (AST, ALT, alkaline phosphatase), liver injury (cholestatic, mixed, hepatocellular), jaundice, which are reversible after discontinuation of the drug.

Nervous system: dizziness, dystaxia, ataxia, confusion, irritability, depression, hyperexcitability, fatigue, insomnia, headache, seizures, hallucinations, peripheral neuropathy.

Urinary system: dysuria, cystitis, polyuria, enuresis, urine staining in red-brown color.

Allergic reactions: skin rash, hives, skin flushing, nasal congestion, fever, anaphylaxis.

Vascular and lymphatic systems: very rarely - agranulocytosis, neutropenia, thrombocytopenia, pancytopenia, leukopenia.

Local reactions: at i.v. administration - thrombophlebitis (pain, redness, edema).

Other: candidiasis, myalgia, arthralgia, visual disturbances.

OVERDOSAGE

Data on drug overdose are missing.

CAUTIONS

With caution to give patients with:

- diseases of the CNS;
- hepatic encephalopathy (to use lower doses);
- impaired hematopoiesis;
- predispose to edemas, patients taking glucocorticosteroids (since the product contains sodium ions).

Note that in the period of the drug administration is contraindicated admission of ethanol, because of development the disulfiram-like reactions (abdominal cramps, nausea, vomiting, headache, a sudden rush of blood to the face).

The drug can immobilize treponemes and lead to the false positive test of Nelson.

At the long term of treatment (10 days or more) is necessary to monitor the blood picture and the development of side effects such as neuropathy (paresthesia, ataxia, seizure, dizziness).

At the development of neurological symptoms, discontinue the using of drug.

In patients on hemodialysis, metronidazole and its metabolites are eliminated within 8 hours. Immediately after dialysis the administration of metronidazole should be repeated.

This product contains 13.96 mmol sodium per 100 ml. To be taken into consideration by patients on a controlled sodium diet.

Pregnancy and lactation

The drug is contraindicated for use in the I trimester of pregnancy and during breastfeeding. With caution to give the drug in II and III trimesters of pregnancy (in case of urgency). Should be used low doses and a short course of therapy.

Effects on ability to drive and use machines

Not recommended to drive a car or operate complex machinery during treatment.

DRUG INTERACTION

At simultaneous use of metronidazole with indirect anticoagulants is marked increase in prothrombin formation time.

At simultaneous use of metronidazole with lithium salt may increase the concentration of lithium in blood plasma and the development of intoxication symptoms.

At simultaneous use with phenytoin or phenobarbital may accelerate excretion of metronidazole from the organism and decrease its concentration in blood plasma.

Metronidazole reduces the clearance of 5-fluorouracil, which may lead to increased toxicity of the latter.

At simultaneous use with cyclosporine may increase the levels of cyclosporine in the blood plasma.

Metronidazole increases the level of busulfan in blood plasma, leading to increase its toxicity (severe form).

At simultaneous use with cimetidine is indicated inhibition of the metronidazole metabolism, which may lead to an increase the concentration of metronidazole in the blood plasma and increased risk of adverse reactions.

Sulfonamides enhance the antimicrobial action of metronidazole.

At simultaneous use with ethanol is indicated a development of disulfiram-like reactions.

Not recommended a simultaneously administration of metronidazole with non-depolarizing myorelaxants (eg, vecuronium bromide), astemizole and terfenadine.

Pharmaceutical interactions

Metronidazole for i.v.administration is not recommended to mix with other drugs.

STORAGE CONDITIONS

Store at temperature below 30 °C in the protected from light place and out of reach of children.

SHELF LIFE

2 years. The drug should be used until the date indicated on the package.

RELEASE FORM

In plastic bags of PVC per 100 ml.

DELIVERY TERMS

Prescription medicine.

MANUFACTURER

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