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FEATURES OF THE LONG-TERM USE OF THE DRUG NIMESULIDE (NIMESIL)

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Abstract
At present, effective pain relief is one of the most important tasks of modern society. Since inflammation is the main cause of the development of acute and chronic pain, non-steroidal anti-inflammatory drugs are most often used in the treatment of rheumatic diseases. To effectively help patients with rheumatic diseases, it is necessary to choose a drug that has a pronounced therapeutic effect from the group of non-steroids, is in demand for rapid development of the effect and good safety. The drug nimesulide (Nimesil) has this property. Non-steroidal anti-inflammatory drugs are used in short courses until pain syndrome and local inflammation decrease, but in patients with persistent activity and signs of the disease, long-term use of these drugs is necessary. When prescribing these drugs for the long term, it is necessary to take into account the risk of cardiovascular, gastrointestinal and kidney pathologies.

Keywords: Nimesulide, nimesil, Syclo-oxygenase -1, cyclo-oxygenase-2 inhibitors, prostaglandin, proton pump inhibitors, hepatotoxic, nephrotoxic effects.

Introduction

Nimesulide has a powerful analgesic, anti-inflammatory and anti-fever effect . It is an approved drug for use in acute pain, symptomatic treatment of rheumatic diseases (including the European Union, South and Central America, China, India and some other Southeast Asia) in more than 50 countries worldwide.

Relieves the symptoms of many diseases. It is a cyclo-oxygenase-2 (COX-2) inhibitor, this enzyme is produced in the inflammatory process and is involved in the synthesis of prostaglandin, which

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is associated with the pathogenesis of pain, inflammation and fever. It is used to treat acute pain, namely rheumatoid arthritis, osteoarthritis, arthritis of various etiologies, arthralgia, myalgia, post-traumatic pain, bursitis, tendonitis, algodismenorrhea, pain relief during toothache, and to reduce inflammation. In osteoarthritis, periarthritis, tendonitis, tenosinovitis, lumbago, muscles, joints and other pathologies of the musculoskeletal system, nimesulide grease and gel form are used. Cyclo-oxygenase enzyme inhibitors weaken the biosynthesis of prostoglandins, resulting in pain relief. Prostaglandin prevents the formation of E2 both in the focus of inflammation and in the afferent pathways of the notsiseptive system, including conduction of pain impulses in the spinal cord. Short-acting prostaglandin reduces the concentration of H2, from which prostaglandin E2 is formed under the action of prostaglandinizomerase. A decrease in the concentration of Prostaglandin E2 leads to a decrease in the level of activation of EP-type PROSTANOID receptors, which have analgesic and anti-inflammatory effects. It has little effect on Cox-1, practically does not prevent the formation of prostaglandin E2 from arachidonic acid under physiological conditions, as a result of which the side effects of the drug are reduced. The drug also reduces platelet aggregation by reducing the synthesis of endoperoxides and thromboxane A2, reduces plasminogen activation and release of histamine in a Free State, and also reduces the level of bronchospasm caused by the action of histamine and acetaldehyde. Tumor necrosis, which leads to the formation of cytokines, weakens the release of factor-A. It has antioxidant properties, prevents the formation of toxic products of oxygen breakdown by reducing the activity of myeloperoxidase. It interacts with glucocorticoid receptors, activating them through phosphorylation, which also enhances the anti-inflammatory effect of the drug. Side effects of nimesulide are similar to other nosteroids, but these have fewer gastrointestinal mucosal irritation features. Unlike selecoxibes, nimesulide does not have the characteristics of a significant side effect on the cardiovascular system. When using nimesulide for less than 10 days, children do not have an increased risk of short-term asymptomatic increase in ketoprofen, paracetamol, aspirin, or ibuprofen compared to hypothermia, gastrointestinal bleeding, epigastral pain, vomiting, diarrhea, or liver enzyme activity. The use of nimesulide is prohibited during pregnancy, while during breastfeeding it should only be used with caution if necessary. The most common of the adverse events associated with the intake of non - steroidal anti-inflammatory drugs are ulcerogenic, Hepato-and nephrotoxic effects, adverse effects of drugs on the cardiovascular system, which significantly limit their long-term use. In rheumatic diseases, these drugs, if used for a long time, require taking these drugs in minimal doses and courses. From this group of drugs, it is necessary to choose a drug that, when used for a long time, has a rapidly manifested anti-inflammatory effect, the analgesic effect is also effective. Also per os should not cause side effects to the gastrointestinal system when applied. When prescribing these drugs to patients, it is necessary to monitor the cardiovascular condition. The risk of gastrointestinal complications increases when using non-steroidal anti-inflammatory drags. This risk can be reduced by the use of selective or partially selective drugs for cyclooxygenase-2 (Cox-2). If the risk of complications is high, a combination of such drugs with a proton pump inhibitor should be used. In modern clinical practice, the most convenient drug for long – term administration is a drug for oral administration that has a partially selective effect on nimesulide-cyclooxygenase-2 (Cox-2), with a low risk of complications of the cardiovascular system and minimal Hepato - and nephrotoxic effects. Nimesulide is very well

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studied and widely used in world clinical practice. The drug is used in almost 50 countries of the world. Nimesil has advantages in terms of low gastrointestinal, cardiovascular side effects, as well as in terms of rapid anti-inflammatory effects, and in terms of effectiveness of analgesic effects. The analgesic property comes to the surface after 30 minutes. The indicated properties of the drug are based not only on reducing the activity of Cox-2, but also on those effects that are not related to the suppression of Cox-2 activity. These effects are also involved in the control of the anti-inflammatory mediators of the drug. They are also associated with the biochemical properties of the drug-the high lipophilicity and alkaline properties of the nimesulide molecule make it difficult for it to penetrate the mucous membrane of the upper gastrointestinal tract. The maximum daily dose of the drug is 200 mg. At the same time, some doctors and patients are known to refuse to use nimesulide due to its negative effects on liver and kidney function. Acute liver failure when taking nimesulide is an unpredictable effect of the drug, which can develop both with long-term use and after a few doses, but it is very rare in patients. One of the most common complications of non -steroids is bleeding from the gastrointestinal tract. According to the results of the tests, the risk of gastrointestinal bleeding was 3.2% when using nimesulide and 5.7% when using meloxicam. It is important to note that, due to the low incidence of Hepato - and nephrotoxic effects and high safety against gastrointestinal and cardiovascular complications, the benefit/risk ratio of nimesulide remains consistently high despite reported cases of acute kidney and liver damage. Patients were given general clinical trials, a general blood test, a general urine analysis, A C-RB Test; total protein, albumin, creatinine, glucose, bilirubin, aspartate, and alanine aminotransferase. In part of the patients, daily proteinuria was examined, renal ultrasound, Doppler examination of the renal arteries was carried out. The therapy patients received at the outpatient stage before hospitalization and the recommendations of their attending physicians after treatment were analyzed. The results were analyzed based on the Mann-Whitney criteria, Wald-Wolfowitz criteria, Wilcoxon criteria, character criteria. The study included 53 patients (men), with an average age of 42.3±10.5 years, with a disease duration of 14.1±8 years (55.2%). Most of the patients had a high activity of the disease. When analyzing the dosage regimen of nimesulide, it was found that 18 patients take the drug from 6 months. Up to 1 year, 12 – 1 to 3 years, 22 – more than 3 years and less than 10 years, more than 6-10 years. 8 patients take the drug several times a year in courses of 10 days, several times in the 12th week, 26 – constantly, 24 patients have found it difficult to clarify the dosage regimen. 24 patients usually take 200 mg of the drug per day, 34-400 mg per day., 12-more than 500 mg per day. In severe pain, 18 (25.7%) patients receive between 500 and 800 mg per day. Thus, 27 of the 70 patients (38.57%) violated the recommended regimen of the drug. 42 patients noted that the attending physician was informed of the possible side effects of the drug and that it is not allowed to exceed its therapeutic doses. 22 patients were observed to have ulcerogenic effects of the drug, 16 – hepatotoxic, 9 – adverse effects on the cardiovascular system, 2-adverse effects on hematopoiesis, 10 – impaired kidney function. It should be noted that all patients take nimesulide together with proton pump inhibitors (omeprazole). Taking this drug along with corticosteroids can increase the risk of bleeding from the stomach and the appearance of ulcers. Taking them together with anticoagulants leads to an increased effect of anticoagulants. Nimesulide attenuates the effects of furosemide and other antihypertensive drugs. Prescribing nimesulide for 24 hours before and after methotrexate

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increases methotrexate concentration. According to an epidemiological study conducted in Italy, against the background of taking nimesulide, gastrointestinal complications were recorded 2 times less than others (nimesulide-10.4%, diclofenac-21.2%, ketoprofen – 21.7%, pyroxycam – 18.6%). Nimesulide has a relatively rare occurrence of hepatotoxicity of the drug, liver complications. According to statistics, complications such as acute liver failure or severe cholestasis occur in one in every 10,000 patients who regularly take nosteroids. Taking nimesil a decrease in pain was recorded in the 20th minute. Soluble granules ensure that the maximum serum concentration of the drug is quickly achieved and accelerate the development of the therapeutic effect. In 43 patients with osteoarthrosis and rheumatoid arthritis with mucosal ulcers, gastric ulcer recurrence was recorded in significantly fewer numbers, showing relatively low rates compared to diclofenac (5.6 and 33.3%, respectively). Toxicity has only been reported from the concomitant administration of nimesulide with other hepatotoxic drugs, atorvastatin, paracetamol, diclofenac, azithromycin, and ceftriaxone. Hepatopathy caused by nonsteroidal anti-inflammatory drugs has a metabolic or immunological specificity. Risk factors for its development are: old age, female sex, pathology of the hepatobiliary system, genetic abnormalities, hypoalbuminemia. Thus, discontinuing the co-administration of hepatotoxic drugs further reduces nimesulide's risk of developing a hepatotoxic reaction. According to statistics, the side effects of this drug on kidney function are very low. Results from domestic and Foreign Studies nimesulide very rarely leads to increased bronchospasm in patients with bronchial asthma, in patients with aspirin asthma and in patients with high sensitivity to anti-nosteroidyallic drugs. As a result of the research carried out, the high efficiency and safety of the drug R. M. Investigations by Balabanova et al examined the efficacy of nimulide in 71 patients with rheumatic disease: rheumatoid arthritis, osteoarthrosis, spondyloarthritis. 18 of these patients have arterial hypertension and receive APF inhibitors, selective beta blockers. In Anamnesis of 2 patients, erosive-ulcerative damage to the gastrointestinal tract and at the time of inclusion in the study, gastroprotective therapy (Ranitidine, omeprazole) was carried out. Nimesulide is prescribed at a dose of 200 mg per day for 30 days. As a result of treatment, a significant improvement in the main ones was noted. The positive effects of therapy were reported by 97% of patients: the good effects were 76% and the satisfactory effects were 21%. Adverse effects developed in 5 (7%) of patients: moderate gastralgia (1), mild nausea (1) and headache (1), with mild heart rate observed. In 1 patient with long-term AG Anamnesis, the dose of nimesulide was discontinued with a reduction of up to 100 mg / day. During the study, no negative dynamics of hemoglobin, erythrocytes, platelets, alanine aminotransferase and aspartate aminotrasferase, bilirubin, creatinine levels were recorded. As a result of the tests, the level of blood pressure in all patients with arterial hypertension remained stable throughout the entire treatment period and did not require additional treatment. In addition, negative interactions with these drugs and the antihypertensive and basic anti-inflammatory drugs that patients took have not been recorded. In a comparative study of the different dosages of nimesulide (nimulide) and its effectiveness and tolerability, experiments on taking it together with other drugs – combination glucosamine sulfate (250 mg) and chondroitin sulfate (200 mg) - have also been confirmed that this drug is safe. Hypersensitivity to the drug, erosive-ulcerative damage of the gastrointestinal tract (in the excitation phase), ulcers, wound perforation or bleeding in the gastrointestinal tract, bleeding from the gastrointestinal tract, asthma with "aspirin", liver failure,

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kidney failure (creatinine clearance-less than 30 ml/min), pregnancy, lactation, fever in acute respiratory viral infections, alcoholism, drug administration is prohibited. Taking nimesulide is not possible for children under the age of 12 due to the possibility of hepatotoxicity. Caution should be used in Arterial hypertension, heart failure, type 2 diabetes mellitus. Elderly patients are not required to reduce the dosage regimen when prescribing the drug. With long-term use, systematic control of the functioning of the liver and kidneys is necessary.

Continuous use of nimesulide for more than 15 days can cause the following side effects, namely stomach ache, nausea, vomiting, diarrhea, gastralgia, itching, bitter taste in the mouth, gastrointestinal mucosa ulcer, headache, dizziness, decreased diuresis, allergic reactions (skin rash, anaphylactic shock), thrombocytopenia, leukopenia, anemia, agranulocytosis, prolonged bleeding time, increased activity of "liver" transaminases, hematuria, unpleasant reactions such as bronchospasm can occur, if any negative reaction occurs, it is necessary to stop taking the drug. Thus, nimesulide (Nimesil) is successfully used in the treatment of chronic and acute pain at a dose of no more than 200 mg per day. . Tablets are taken at room temperature, with a sufficient amount of water after meals. Granules (powder) — one package of Nimesil is thoroughly mixed in 100 ml of water at room temperature and drunk immediately, it is not recommended to drink after taking it after mixing with water. Gel is applied externally. About 3 cm is applied to the affected area and applied slightly, repeated 3-4 times a day. The gel should not be rubbed hard or use bandages. The duration of therapy is determined individually. Symptoms of an increase in the amount are: drowsiness, nausea, vomiting, pain in the epigastric area, gastrointestinal bleeding, arterial hypertension, acute kidney failure, respiratory depression, anaphylactic reactions, coma. There is no special antidote. Symptomatic therapy should be performed when overdosing. For the first four hours, patients should wash the stomach and consume activated charcoal. Anticoagulants can enhance the effects of anticoagulants when used with nimesulide. If it is not possible to prevent such combined therapy, it is necessary to carefully monitor the blood clotting indicators. Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists may weaken the effect. In some patients and in the presence of cases of impaired renal function, the simultaneous use of these substances can lead to a further deterioration in kidney function and the appearance of acute kidney failure. It is necessary to be very careful when using such a combination, especially in elderly patients. Nimesulide temporarily weakens the effect of Furosemide on sodium elimination and to a lesser extent eliminates potassium, as well as reducing the diuretic effect. Simultaneous use of Furosemide and nimesulide in patients with impaired renal or cardiac function requires caution. Nimesulide can increase the nephrotoxicity of cyclosporine. In patients who use nimesulide, the drug should be discontinued when body temperature rises or flu-like symptoms appear. During treatment with nimesulide, no serious reactions were observed by the liver. But patients who have symptoms similar to liver damage such as anorexia, nausea, vomiting, abdominal pain, weakness, dark urine color, or whose liver function laboratory test data deviate from the norm, should stop taking the drug. During treatment with nimesulide, the patient should not use other analgesics. In patients at risk of ulcers, bleeding, treatment should be started with the lowest possible effective dose. For these patients, combined therapy should also be carried out using protective agents such as proton pump inhibitors. Patients who take concomitant medications that increase the risk of ulcers or bleeding, such as corticosteroids, anticoagulants, acetylsalicylic

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acid, should be warned about the need to be careful when using nimesulide. Treatment with the drug should be discontinued if the patient who received nimesulide has bleeding or ulcers in the digestive tract. Patients with Crohn's disease or ulcerative colitis should be prescribed with caution, since nimesulide can lead to their exacerbation. Nimesulide oral contraceptives, anticoagulants can exacerbate other diseases of the digestive tract.

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