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JUVENILE IDIOPATHIC ARTHRITIS IN CHILDREN: A MODERN VIEW OF THE PROBLEM.

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SUMMARY. *The article presents data on the comparative effectiveness of traditional therapy and chronotherapy in the treatment of juvenile rheumatoid arthritis. The recommended nimesulide by the method of chronotherapy has shown its effectiveness not only in relation to early arthritis, but also in patients with a long history. This was expressed in accelerating the onset of remission and its prolongation, reducing side effects of drug therapy.*
Keywords: *juvenile idiopathic arthritis, prognosis, chronotherapy.*

Relevance

Juvenile idiopathic arthritis (JIA) is among the most severe and chronic form of socially significant Patolo ology in children. Over the past 10-15 years, certain successes have been achieved in the treatment of this pathology. However, not all problems have been resolved. Statistics indicate a high percentage of children with a long-term progressive course of the disease, with functional insufficiency, with signs of drug illness caused by antirheumatic drugs.

The literature analysis indicates the aggressiveness and high likelihood of disability in children with juvenile rheumatoid arthritis [1,4,8]. Traditional therapy of the disease is far from always effective, which necessitates the search for new effective methods of treating this disease.

The method of chronotherapy allows to increase the effectiveness of treatment while reducing the doses of the drugs used, as a result of which their side effect is reduced and treatment is cheaper [6]. The main goal of pathogenetic therapy is to slow the progression of the disease and achieve remission. However, unfortunately, it does not always provide quick relief of pain, so the use of symptomatic analgesics is absolutely justified in the complex treatment of RE. Analgesics play the role of "first-stage" therapy, which is prescribed in the debut of the disease. In the future, their use continues to ensure a satisfactory quality of life for the patient [5]. Among the symptomatic painkillers used in rheumatology, a special place belongs to non-steroidal anti-inflammatory drugs (NSAIDs). According to modern ideas, the positive therapeutic effects of NSAIDs are associated with their ability to inhibit COX-2, while the most common side effects (gastrointestinal tract, kidney damage, impaired platelet aggregation, etc.) are associated with suppression of activity COX-1 [7].

In recent years, scientific research on chronotherapy has intensified abroad. The results of scientific research indicate the high effectiveness of this treatment method. It should also be noted that JIA predisposition loci may be associated with other autoimmune diseases. This hypothesis is supported by cases of JIA associated

with autoimmune diseases such as type 1 diabetes mellitus (DM) [4], autoimmune thyroiditis [5], and celiac disease [6]. The genetic component makes a significant contribution to the development of JIA. Twin methods of genetic analysis showed a 25–40% degree of JIA concordance in identical twins, which is significantly higher than the incidence of this disease in the general population, reaching an average of one case per 1000 people [7], while the incidence of JIA in sibling couples is approximately 15– 30 times higher than the prevalence of JIA in the general population [4].

Juvenile idiopathic arthritis predisposition genes identified by screening for loci previously associated with rheumatoid arthritis. Using the method of whole genome scanning, a lot of genetic variants have been discovered, each of which is involved in the pathogenesis of several autoimmune diseases. Since the molecular mechanism of the pathogenesis of autoimmune and inflammatory diseases has a number of similar features, they may also share common susceptibility genes. In this regard, geneticists began to study the loci, for which association with such an autoimmune disease as RA was proved, for a possible connection with JIA.

Alimov A.V. (2002) found that in acute pneumonia in newborns in the second half of the day, a more pronounced destabilization of cell membranes, increased phagocytic activity of leukocytes, which causes the accumulation of infectious biomass at a specified time, are determined. This is the basis for the appointment of higher doses of antibiotics in the afternoon and at night [2].

Chronotherapy contributes to the further development of the principle of an individual approach to the treatment of patients, which is especially important in pediatrics. Studies on the development of a chronopharmacological approach to the treatment of rheumatoid arthritis with modern NSAIDs were not found in the analysis of the literature, which prompted this study.

Purpose of the study. To study the comparative effectiveness of the use of COX-2 inhibitors by the method of chronotherapy and traditional therapy in the treatment of patients with juvenile rheumatoid arthritis.

Materials and methods

The study included 84 patients with JRA : 47 boys and 37 girls aged 2 to 16 years (mean age 11.2 ± 0.8 years). Of all the examined 74 (88.1%) children with articular form and 10 (11.9%) children with articular-visceral form of the disease. The duration of the disease ranged from 3 months to 8 years.

The work used clinical, laboratory, instrumental and functional research methods. Features studied in detail clinical variants of Jura, a comparative analysis of the effectiveness of traditional therapy of Jura and chronotherapy with COX-2 inhibitors using the criteria of the American College of Rheumatology (ACR).

The main group consisted of 54 patients treated with the inhibitor s COX- 2 by chronotherapy, the control group - 30 children with JRA who are on conventional therapy. The diagnosis of juvenile rheumatoid arthritis was established based on the classification criteria of the Jura of the American College of Rheumatology.

Evaluation of the activity of the disease and the effectiveness of therapy was carried out on based on the definition of the number of joints with exudation, painful and active joints (with exudation, pain and / or stiffness), joints with impaired function, Ritchie pain index, the number of systemic manifestations per patient and the DAS4 (Disease Activity Score) index calculated by the formula: DAS4 = 0.54 * sqrt (Richie index) + 0.065 * (number of swollen joints) + 0.33 * Ln (ESR) + 0.007 * (general assessment of the state of health according to the patient on a 100-mm visual-analogue scale).

From laboratory tests: general blood count, rheumatoid tests, rheumatoid factor, daily dynamics of cortisol in the blood. The analysis of daily thermometry indicators is carried out.

Result and discussion

It was established that out of 74 patients with the articular form of the disease, 52.7% of patients had an oligoarthritic variant, 47.3% had a polyarticular one. In 12 patients observed by us, a persistent variant of oligoarthritis was noted, which was

characterized by the fact that up to 4 joints were affected during the entire period of the disease. Two patients (2.7%) developed ankylosis in the joints of the wrist, and 1 (1.4%) patient developed destructive arthritis.

The articular-visceral form was observed in 10 (11.9%) of the patients examined by us and was clinically characterized by a high temperature reaction that was intermittent in nature and did not decrease during antibiotic treatment. In these children, an increase in the size of the liver and spleen was noted. In 4 (40%) patients, the disease proceeded with kidney damage, in 5 (50%) patients with heart damage, in 1 (10%) - with lung damage, in 2 (20%) - combined injuries of internal organs were noted.

Rheumatoid activity evaluation process using index DAS 4 we carried out considering clinical guidelines E.L.Nasonova: 1st degree of activity was aevaluated at the values DAS 4 <2.4 units 2nd degree of activity was characterized by values in a range of 2.4 < DAS 4 <3.7 units, respectively, 3rd degree - with DAS 4> 3.7 units. It was revealed that the average DAS 4 values in the groups approximately corresponded to the established boundaries (Table 1).

Indicators of activity of the rheumatoid process using the DAS 4 index in the examined patients.

Indicator	1st degree of activity	2nd degree of activity	3rd degree of activity
Das4	1.37 -2.29	2.48-3.7	3.71-4.54

The calculation of the DAS 4 indicator in dynamics, even in the absence of significant differences with the initial value, established a higher level of activity. An intragroup analysis of DAS 4 indicators found that in the group of patients with minimal activity, the parameters did not change significantly or tended to decrease in most children. In patients with the 2nd degree of activity in 19 (59.3%) cases an increase in DAS 4 was detected , in 13 (40.6%) cases there was a slight decrease or absence of parameter changes.

In patients with the 3rd degree of activity in 4 (44.4 %) cases, there was a significant increase in DAS 4 in parallel with an increase in activity (ESR from 46 to 50 mm / hour, CRP from 6 mg /% to 36 mg /%,) and the number of patients with polyarthritis. In 5 (55.6%) cases, DAS 4 values did not change significantly or tended to slightly decrease.

An analysis of the timing of remission shows that in the vast majority of patients 69 (82.1%), the average duration of remission is 4 months, with no dependence on the degree of activity of the disease. This indicates that the therapy does not lead to complete clinical and laboratory remission, resulting in frequent relapses and disease progression.

The majority of 69 (89.1%) of the patients examined by us had a seronegative variant of JuRA. This is consistent with literature data, according to which the incidence of rheumatoid factor in children is 15-20%. Hypochromic anemia was noted in 53 (63.1%) patients . In more than half of the patients examined by us, 53 (63.1 %) had the first stage of anatomical changes according to Steinbrocker, i.e. - epiphyseal osteoporosis, in 27 (32.1%) - revealed a narrowing of the joint space and the presence of single erosion. Cartilage and bone destruction occurred in three patients with a disease term of more than 3 years. Ankylosis formed in one sick girl with Still's syndrome.

The analysis of clinical, laboratory, instrumental and functional methods for the study of patients with juvenile rheumatoid arthritis indicates the aggressiveness and progressive nature of the disease , which reflects the modern age related evolution of the disease, which necessitates the search for effective methods of treatment for this disease.

All patients with articular-visceral form received prednisone and NSAIDs, 80% of them included methotrexate in the complex treatment. 54 (64.3%) patients with the articular form received prednisone, methotrexate in 3 (4.1%) patients, nonsteroidal anti-inflammatory drugs from COX-1 inhibitors were recommended for all patients with JuRA.

Side effects from taking COX-1 inhibitors were noted in most patients with a disease duration of more than 3 years, which were characterized by damage to the gastrointestinal tract and liver.

Chronotherapy with nimesulide was recommended to 54 patients with JuRA. As a simple and very affordable criterion for choosing the time of administration of NSAIDs in a particular patient with juvenile juvenile disease, we used the acrophase of body temperature, since the maximum temperature amplitude indicates the degree of activity of the inflammatory process. For this, we performed daily thermometry in 84 observed patients with juvenile anemia. Analysis of daily thermometry in patients with juvenile arthritis shows that there are two peaks of fever, observed in the morning at 8 o'clock and in the afternoon from 14 to 18 o'clock. Confirmation of the peak of the inflammatory process is also our data on the dynamics of the level of cortisol in the blood in patients with juvenile juvenile disease. A study was made of the level of cortisol in the blood of 35 patients with juvenile disease. The dynamics of the level of cortisol in the blood was determined in the morning (8^{00}) and in the afternoon (14^{00}). When choosing the time of blood sampling, the cortisol content was guided by the dynamics of daily thermometry. The control group consisted of 10 healthy children. The dynamics of the level of cortisol in the blood of patients with juvenile are presented in table 2

Table 2.

The dynamics of the level of cortisol in the blood of patients with juvenile

Indicators	Patients Jura		Healthy children n = 10
	8^{00} in the morning n = 35	14^{00} days n = 35	
Cortisol level (nmol / l)	301 ± 27.9 *	351 ± 32.7 *	89 ± 7.8

*Note: * - data reliability in comparison with healthy children (P <0.001)*

Normally, the maximum level of cortisol in the blood is observed in the morning, usually from 6 to 9 in the morning, then it gradually decreases and in the evening the level of cortisol drops to a minimum mark. In patients with JRA, we noted significant fluctuations in the level of cortisol in the blood in the morning from 56 nmol / l to 532 nmol / l. In the afternoon, the second peak of the rise in the level of cortisol in the blood was observed, exceeding the average morning indicators. The dynamics of cortisol levels correlated with daily thermometry. One patient showed low levels of cortisol in the blood: in the morning - 59 nmol / l, in the afternoon 41nmol / l. Given the duration of the disease in this patient (7 years) and the severity of the form (articular-visceral), the decrease in cortisol in the blood was regarded as a sign of adrenal cortex insufficiency, observed in severe cases of autoimmune diseases.

Considering that the majority of patients observed by us in the morning received hormone therapy with prednisolone, which has an anti-inflammatory effect, we, according to chronotherapy, recommended COX-2 inhibitors in patients with second acrophase of body temperature.

The effectiveness of the treatment of COX-2 inhibitors was evaluated according to clinical and laboratory studies. Clinical and laboratory parameters were evaluated before the start of the study and after 2-4-6-8 weeks. During therapy with COX-2 inhibitors, a marked improvement was noted in the joint syndrome in the form of a decrease in the number of joints involved in the process, relief or reduction of arthralgia, a decrease in the duration of morning stiffness, and an increase in the range of motion in the joints (Table 3).

Already after the first two weeks of using COX-2 inhibitors, 57.4% of patients showed an ACR20 response, 24.1% of patients showed an ACR of 50, and 3.7% showed an ACR70. By the 8th week, the effectiveness of the drug was observed in

80% of patients, of which ACR20 response was achieved in 15%, ACR50 in 35%, ACR70 in 30%. In addition, there was an improvement in the well-being of patients, an increase in overall activity, a decrease in the severity of symptoms of intoxication, and a decrease and normalization of laboratory activity indicators . In 44 patients with the articular form of the disease and 10 with the systemic form of Jura who completed the treatment of COX-2 inhibitors, the dose of glucocorticosteroids was reduced. The average daily dose of prednisone at the 8th week of COX-2 inhibitors COX-2 inhibitors was effective not only against early arthritis, but also in patients with a long history. Given the good response to therapy, 11 children received prolonged therapy of COX-2 inhibitors.

The results confirm the efficacy and safety of COX-2 inhibitors in the treatment of refractory, long-lasting Jurassic. After 6 months in patients who received COX-2 inhibitors in complex therapy, the disease activity significantly decreased. They reliably ($P < 0.05$) decreased the number of joints with exudation and painful joints, decreased the Richie index and the value of the DAS4 index.

Table 3

Characterization of the comparative effectiveness of chronotherapy of COX-2 inhibitors and traditional therapy in the treatment of juvenile rheumatoid arthritis

Indicator	With chronotherapy nimesulide		With traditional therapy	
	Before treatment	After treatment	Before treatment	After treatment
The number of joints with exudation	8.3 ± 1.04	4.3 ± 0.8 *	8.6 ± 1.2	5.8 ± 0.9
Number of painful joints	7.8 ± 1.01	2.3 ± 0.5 *	7.9 ± 1.4	4.9 ± 0.6

Richie Index	15.6 ± 2.2	9.3 ± 0.8 *	16.1 ± 1.7	12.5 ± 1.2
Number of active joints	9.8 ± 1.1	15.6 ± 1.3 *	10.1 ± 1.2	12.3 ± 1.3
The number of joints with impaired function	8.2 ± 0.9	2.4 ± 0.6 *	7.9 ± 1.1	5.7 ± 0.9
DAS index 4 number of systemic manifestations per 1 patient	3.7 ± 0.4	2.6 ± 0.7 *	3.6 ± 0.3	3.4 ± 0.3
ESR, mm / h	22.5 ± 1.7	12.6 ± 0.5 *	20.3 ± 2.7	16.3 ± 0.8
The level of CRP, mg%	17.2 ± 3.4	4.8 ± 1.2 *	16.8 ± 3.7	8.6 ± 1.5

*Note: * - the reliability of the data compared with indicators before treatment and after (P <0.05)*

A significant decrease in the number of systemic manifestations per patient was also noted. These patients stopped febrile fever, positive dynamics of carditis, polyserositis.

Follow- up observation of patients indicate a more persistent and prolonged remission, which is an average of 8 months. Moreover, the complaints of patients indicating the side effects of NSAIDs were significantly reduced. This gives grounds to consider chronotherapy as COX-2 inhibitors in patients with juvenile arthritis more optimal and safe treatment.

Thus, chronotherapy with COX-2 inhibitors turned out to be clinically effective and led to a decrease in the activity of JuRA, confirmed by the dynamics of the corresponding clinical and laboratory markers. Our experience allows us to suggest the possibility of more active use of chronotherapy with COX-2 inhibitors in the treatment of juvenile rheumatoid arthritis.

Conclusions

1. The study of the dynamics of the clinical manifestations of Jura has made it possible to establish the progressive nature of the disease with damage to many organs

which indicates the refractoriness of the disease to traditional therapy.

2. The use of the inhibitor s COX-2 by chronotherapy in patients with JRA increased the effectiveness of therapy, which is expressed in the acceleration of remission, lengthening its duration and reducing the side effects of drug therapy.

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