Some clinical and economic aspects of pharmacotherapy in patients with chronic pancreatitis and osteoarthritis

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Key words: pharmacotherapy, economic costs, clinical and economic analysis, chronic pancreatitis, osteoarthritis, nonsteroid anti-inflammatory drugs (NSAIDs)

In recent decades, in the Russian Federation, on the rise, there is the incidence of diseases of the musculoskeletal system in general, and in particular osteoarthritis [1, 3, 11], which corresponds to the global trends [1, 4]. As it is known about symptomatic treatment of pain in patients with osteoarthritis (OA), nesteroid anti-inflammatory drugs (NSAIDs) are the basis. Due to the high prevalence in the population both osteoarthritis, and chronic pancreatitis (CP) [13, 17], in patients at the same time there is a cohort of individuals with both these nosologies.

In previously published papers [1, 2, 15, 16] presented the results of studies of the course of HP in patients receiving NSAIDs. In addition to clinical questions, we are interested in the economic aspect of the use of NSAIDs in patients observed. Methodology of clinical and economic analysis is a comparative evaluation of methods of prevention, diagnosis, medication and other treatment options based on a comprehensive account of the results of a related medical intervention and the cost of its implementation [4, 7].

The aim of the study is to determine the medical preparation from the group of NSAIDs providing not only the optimal therapeutic effect in the treatment of OA, but the preparation course application which significantly reduces the risk of exacerbation of underlying disease — CP, and therefore in the financial costs of such a treatment and the patient.

Materials and methods.

The study included 58 individuals suffering from both OA and HP. As an alternative interventions to compare the efficacy of NSAID therapy we took selective COX-2 inhibitor (meloxicam) and non-selective inhibitor of COX-1 (diclofenac).

Patients were divided into two groups:

• Group 1 — persons receiving therapy by one of the diclofenac drugs (100 mg per day) — 26 people;

• Group 2 — persons receiving therapy by one of the meloxicam drug (15 mg daily) — 32 people.

Research excluded patients who took aspirin and glucocorticosteroids, patients with diabetes, injuries and tumors of the pancreas, calculus in the gallbladder and bile ducts, symptoms of kidney and liver insufficiency.

In terms of the reliability of the final results of the study was to provide an environment of uniformity compared groups of the main factors, as that identified by gender and age. Table 1 shows that between the groups is not statistically significant differences by gender structure and the average age ($p>0.1$). Duration of NSAID is not less than three months prior to the aggravation of CP.

Personal registration card of clinical and economic studies in addition to information about the age and sex of the patient contained clinical information (primary diagnosis, comorbidities, risk factors), information on ongoing NSAID therapy (drug daily dose), the result of blood serum analysis.

Statistical analysis was performed by Microsoft Office Excel and Statistica 6.0, using the methods of multivariate regression, analysis of variance, the calculation of partial coefficients between the studied phenomena. When necessary (small sample, abnormal distribution of feature in a number of variations), a statistically significant difference between treatment groups on the observed performance was assessed by Wilcoxon-Mann-Whitney U criterion [2] Comparing the mean values of continuous variables with a normal distribution of variables, we used parametric statistical methods; in particular, calculated the Student t-test. The same criterion was used to evaluate the statistical significance of the difference lobes. Statistical significance of the differences between the compared sets of the character of the distribution was assessed by the λ criterion [5, 6]. Differences were considered significant at a value λ, equal to and/or greater than the critical value 1.36.

Data on the cost of the drugs were taken from the price list of the regional distributor of CV "Protek" on December 31, 2014.

Results and discussion.

As "soft" indirect clinical criteria effectiveness of therapeutic intervention in this study was taken frequency of exacerbations HP within a year. The presented in Table 2 data clearly show that meloxicam was significantly more effective in the context of reducing the frequency of exacerbations in patients with OA of CP than diclofenac.

As has been shown in previous studies [12, 15, 16], the use of NSAIDs in the treatment of ambulatory patients with OA and CP significantly affects the number of parameters (amylase, alkaline phosphatase, lipase, lactate dehydrogenase (LDH) aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, interleukin 6(IL-6), C-reactive protein) in the serum of patients with CP during an exacerbation.

As part of the clinical and economic analysis as direct clinical efficacy criteria were taken NSAIDs share patients who during acute CP individual values of amylase, alkaline phosphatase, lipase, AST, ALT, LDH, and profiles of IL-6 and C-reactive protein levels were above the limit values (50 percentile in the corresponding variational series). In six of the nine indicators observed, the proportion of persons with individual values above percentile 50 in the group of patients taking diclofenac, was significantly higher than in the group of patients treated in the outpatient setting meloxicam (Table 3).

To calculate the costs taken into account the cost of pharmacotherapy of NSAIDs for the duration of a standard course of treatment — 3 months, i.e. the product of the average daily dose, and the number of days of average cost of 1 mg. Details are presented in Table 4 and 5.

As seen from the data of Table 4 and 5, drug diclofenac pharmacotherapy turned out to be the least expensive: the average cost of treatment was 476.1 rubles at a minimum and maximum value, respectively: 60.4 rubles (Diklogen; Adzhio

Pharmaceuticals Ltd. — India) and 2863.5 rubles (Voltaren, Novartis Pharma AG — Switzerland / Novartis Pharma SpA / Italy).

Pharmacotherapy by drugs meloxicam was significantly more expensive: the average cost of the patient treatment 1519.6 rubles at a minimum and maximum value, respectively: 524.9 rubles ("Synthesis", Russia) and 5222.5 rubles (Boehringer Ingelheim Pharma GmbH, Germany).

In clinical studies of the economic costs were taken into account in the framework of mandatory health insurance (MHI) for the treatment of patients with acute exacerbation of CP during this period, as well as costs under MHI for outpatient follow-up (regulated by "Agreement on tariffs for the payment of medical care for compulsory health insurance in the territory of the Omsk region" between the Ministry of Health of Omsk region and territorial funds of Omsk region). In the study, the average length of hospital stay was taken to be (on average) of 10 days.

In accordance with this the cost of one-day-stay in the department of gastroenterology, patient profile is estimated at 1274.2 rubles. With an average duration of hospital treatment of the patient with chronic pancreatitis — 10 days, the cost per case of hospitalization is 12742 rubles. In addition, the reimbursement of medical institutions on "finished case" in connection with the hospitalization of patients with CP MHI allocated additional 4835.8 rubles, provided that the standards of treatment are observed [9], i.e. one case of hospitalization of patients with CP, due to the worsening "costs" 17577.8 rubles.

It should be remembered that a patient with CP and OA is under medical observation; and visits throughout the year at least 3 times a year, therapist, rheumatologist and gastroenterologist once. Also, there will be a regulated minimum of laboratory studies [8, 10] (complete blood count, biochemical blood analysis, coprogram), with a total cost of MHI — 2983.39 rubles, I (Table 6).

Thus, the cost under the MHI on the monitoring and treatment of a patient with CP and OA, based on the average number of exacerbations per year reported in Table 2, were:

diclofenac: 2983.39+3.72*17577.8=68372.81 rubles (per year);

meloxicam: 2983.39+2.47*17577.8=46100.56 rubles (per year).

Consequently, the savings due to the use of meloxicam drugs on an outpatient basis in a patient with a combination of OA and CP is 21,972.25 rubles.

Of course, one could argue that the patient often gets medication through personal funds (except those privileged categories), but we must not forget that after acute HP, the patient will be forced to buy medicines of gastroenterological profile, the cost of which incommensurate above course taking NSAIDs.

Upon choosing NSAIDs, these patients must take into account not only the cost of a course of the drug, but performance and cost-effectiveness of therapeutic treatment.

Table 1

Characteristics of the examined patients by age, gender and severity of acute HP

Groups / **Indicators**	**Patients who took diclofenac (N = 26)** $\tilde{X}$ ± mx	**Patients who took meloxicam (N = 32)** $\tilde{X}$ ± **mx**	**Relevance of difference (t / p)**
Age, years	57, 1 ±2,0 = 30 Min / Max = 6 9	54, 6 ±1,5 Min = 34 / Max = 6 9	1.0 /> 0.1
Sex	Men: 15 (57.7%) Women: 11 (42.3%)	Men: 18 (56.3%) Women: 14 (43.7%)	0.11 /> 0.1

Table 2

The number of exacerbations HP, depending on type of NSAID

Indicators		**NSAIDs**		**t / p**
		Diclofenac	**Meloxicam**	
Exacerbations HP (number / year)	N	25	32	5,1 / <0,001
	$\tilde{X}$	3.72	2.47	
	± mx	0.2	0.14	

Table 3

Some values of the investigated parameters of blood serum in acute CP in patients with OA

(percentage of people with individual values above percentile 50, in %)

Groups / IDICATORS	Patients with CP, taking diclofenac (N = 26)	Patients with CP, taking meloxicam (N = 32)	Relevance of difference (t / p)
Amylase	38,5 ± 0,9	0,9 ± 0,01	4.0 / <0.0 01
Alkaline phosphatase	53,8 ± 1,0	1,0 ± 0,1	4.9 / <0.0 01
Lipase	42,3 ± 1,0	15,6 ± 0,4	2.3 / <0.05
LDH	50,0 ± 1,0	9,4 ± 0,3	3.6 / <0.0 01
C-reactive protein	38,5 ± 0,9	40,6 ± 0,8	0 2 /> 0.1
IL -6	30,8 ± 0,9	31,3 ± 0,7	0, 04 /> 0.1
ALT	53,8 ± 1,0	21,9 ± 0,6	2.6 / <0.05
AST	26, 9 ± 0, 8	34, 4 ± 0, 7	0, 6 /> 0.1
Glucose	61,5 ± 0,9	18,8 ± 0,5	3.6 / <0.0 01

Table 4

Calculating the cost of treatment (90 days / 3 months)

by diclofenac preparations (based on 100 mg per day of treatment)

Medicine			Price (RUB):		
Trade name	**Doze, package**	**Manufacturer country**	**Package**	**1 day treatment**	**course treatment**
Voltaren	50 mg №20	Novartis Pharma AG — Switzerland / Novartis Pharma SpA / Italy	318.16	31.82	2863.5
Diclogen	50 mg №50	Agio Farmatsevtikalz Ltd — India	16.76	0.67	60.4
Diclofenac	25 mg	"Biosynthesis" — Russia	9.59	1.28	115.04

	№30				
Diclofenac	50 mg №20	Hemofarm AD — Serbia	34.37	3.44	309.3
Diclofenac	50 mg №20	Hemofarm AD — Serbia / "Hemofarm" -Russia	41.86	4.19	376.7
Diclofenac	50 mg №20	Company "Ozone" — Russia	16.41	1.64	147.66
Diclofenac	50 mg №30	M.J. Biopharm Pvt.Ltd — India	12.19	0.81	73.16
Diclofenac	25 mg №30	"Irbit Chemical and Pharmaceutical Plant " — Russia	24.59	3.28	295.02
Diclofenac	50 mg №20	Hemofarm Group AD — Serbia and Montenegro	34.25	3.42	308.21
Diclofenac-UBF	50 mg №20	Hemofarm Group AD — Serbia and Montenegro / "Hemofarm" — Russia	41.86	4.19	376.74
Diclofenac-FPO	25 №30	"Uralbiofarm" — Russia	11.06	1.47	132.66
Diclofenac-FPO	25 №20	"Pharmaceutical Company Obolensky" — Russia	53.45	10.69	962.10
Naklofen	50 mg №20	"Pharmaceutical Company Obolensky" — Russia	83.16	8.32	748.44
Ortofen	50 mg №20	Krka, dd, Novo mesto — Slovenia	77.62	7.76	698.54
The minimum cost of a course of drug treatment		Diclogen; Agio Pharmaceuticals Ltd — India			60.4
The maximum cost of		Voltaren; Novartis Pharma AG — Switzerland/			2863.5

a course of drug treatment	Novartis Pharma SpA / Italy	
The cost of the course of treatment average		**476.13**

Table 5

Calculating the cost of treatment (90 days / 3 months) by drugs

Meloxicam (at 15 mg per day of treatment)

Medicine			**Price (RUB):**		
Trade name	**Doze, package**	**Manufacturer country**	**Package (average)**	**1 day treatment**	**course treatment**
Movalis	7.5 mg №20	Boehringer Ingelheim Pharma GmbH,Germany	580.3	58.0	5222.5
Movalis	15 mg №20	Boehringer Ingelheim Pharma GmbH,Germany	683.0	34.2	3073.4
Teva-Meloxicam	7.5 mg №20	TEVA, Israel	168.7	16.9	1518.3
Teva-Meloxicam	15 mg №20	TEVA, Israel	248.7	12.4	1119.2
Mirloks	7.5 mg №20	Grodzisk Pharmaceutical Works Polfa Co. Ltd. (Poland)	193.0	19.3	1737.1
Mirloks	15 mg №20	Grodzisk Pharmaceutical Works Polfa Co. Ltd. (Poland)	279.4	14.0	1257.3
Artrozan	7.5 mg №20	"Pharmstandard" Russia	88.9	8.9	800.1
Artrozan	15 mg №20	"Pharmstandard" Russia	211.3	10.6	950.7
Movasin	7.5 mg	"Sintez" Russia	73.3	7.3	659.9

	№20				
Movasin	15 mg №20	"Sintez" Russia	116.6	5.8	524.9
Amelotex	7.5 mg №20	"PharmFirma Sotex" Russia	93.5	9.4	841.9
Amelotex	15 mg №20	"PharmFirma Sotex" Russia	117.8	5.9	530.1
The minimum cost of a course of drug treatment		"Sintez" Russia			524.9
The maximum cost of a course of drug treatment		Boehringer Ingelheim Pharma GmbH, Germany			5222.5
Average cost of the course of treatment					**1519.6**

Table 6

Costing (within MHI) of outpatient care during the year of a patient with OA and CP

№ p / p	**Name of consultation (reception) of specialist or the type of laboratory research**	**Cost (RUB)**
1.	Therapy precinct (including family medicine) *	643.2
2.	Rheumatology	278.1
3.	Gastroenterology	245.8
4.	General blood analysis	179.71
5.	General urine analysis	167.64
6.	Biochemical analysis of blood (including ALT, AST, total protein, albumin, amylase, total bilirubin and direct gamma glutamyl transpeptidase, glucose, C-reactive protein, alkaline phosphatase)	1078.94
7.	Coprogram	270
	Diastase of urine	120

Note. * The table shows the price of 3 times visiting specialist during 1 year (the cost of a single visit 214.4 rubles).

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The comparative clinical and economic analysis of the application of nonsteroid anti-inflammatory drugs (NSAIDs) in patients with with chronic pancreatitis (CP) and osteoarthritis. Meloxikam appeared more effective, than diclofenac, in the context of decrease in frequency of exacerbations of chronic pancreatitis at sick osteoarthritis; and also more significantly I influenced blood serum indicators in the period of CP aggravation. Despite more expensive course, treatments meloxsikam, the economy caused by reduction of frequency of aggravations of CP and consequently also material inputs at the patient with a combination of OA and CP, makes 21972,25 rubles. At a choice of nonsteroid anti-inflammatory drugs at such patients it is necessary to consider not only the cost of course drugs, but indicators of therapeutic and economic efficiency of therapy.