Certain Indicators of Diclofenac Sodium Pharmacokinetics in Patients with Rheumatoid Arthritis Considering Comorbide States

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Abstract

Introduction: Much attention is paid to pharmacokinetic (FK) researches for studying the processes of supply, distribution, biotransformation and excretion of medications at the present time, as well as identifying links between medical substances concentration and (or) its metabolites in biological fluids and tissues, and its pharmacological effect. In the treatment of rheumatoid arthritis (RA), non-steroidal anti-inflammatory drugs (NSAID) are widely used for a symptom therapy, where Diclofenac Sodium (DS) is most commonly prescribed. Duration of anti-inflammatory effect, effectiveness of NSAID in whole are directly dependent on the level of effective concentration of medications and circulation duration in blood in free form.

The Aim of the present research work is to study in a comparative aspect certain indicators of Diclofenac Sodium pharmacokinetics in patients with rheumatoid arthritis with gastric microbiocenosis disorders (gastric dysbiosis) and without disorders (without dysbiosis).

Materials and Method: 38 patients at the age from 18 to 60 years were examined, with I-II-III degree of disease activity. In addition to the general clinical examination, an immune-enzyme method and urease test were carried out to determine Helicobacter Pylori and highly effective liquid chromatography to determine Diclofenac pharmacokinetics.

Results: Conducted researches and analysis of their results indicate that in conditions of rheumatoid arthritis, particularly, in the presence of comorbid states, there is a decrease in the metabolism rate and an extension of NSAID half-excretion period, which increases the risk of side effects, especially to the gastrointestinal tract, and significantly affects the disease course and the results of the treatment.

Conclusion: In conditions of rheumatoid arthritis with comorbid states, there is more frequent occurrence of the NSAID side effects. Research conducted and analysis of their results indicate that in conditions of rheumatoid arthritis, particularly at comorbid states, there are reasonable changes in the NSAID pharmacokinetics. The decreasing of metabolic rate and the extension of the NSAID half-excretion increases the risk of side effects, especially on the side of the GIT, which significantly affects the disease course and results of the treatment. This circumstance dictates the need to take these results into account in the treatment of the studied pathology and in the development of a personalized approach to the treatment of rheumatoid arthritis.

Keywords: *Rheumatoid arthritis, Diclofenac Sodium, highly-effective liquid chromatography, pharmacokinetics.*

Introduction

Now a days a greatattention is paid to pharmacokinetic (FK) researches for studying the processes of supply, distribution, biotransformation and excretion of medications, as well as identifying links between medical substances concentration and (or) its metabolites in biological fluids and tissues, and its pharmacological effect. Clinical pharmacokinetics determines which dosage of medicines provides their necessary concentration in body media to achieve optimal therapeutic effect. For the present time several method for determining Diclofenac in biological fluids are known: potentiometric analysis[1], highly effective liquid chromatography (HELC)[2], capillary zone electrophoresis[3], spectrophluometry[4], thin layer chromatography[5], polar-graphic analysis[6].

It is generally known that in the treatment of rheumatoid arthritis (RA), non-steroidal anti-inflammatory drugs (NSAID) are widely used for a symptom therapy, where Diclofenac Sodium (DS) is most commonly prescribed. Duration of anti-inflammatory effect, effectiveness of NSAID in whole are directly dependent on the level of effective concentration of medications and circulation duration in blood in free form. These parameters in clinical practice determine a number of pharmacokinetics indicators, in particular, Cel (constant of elimination), Cl (medication clearance), T1/2 (half-excretion of medication), etc. In human body Diclofenac undergoes biotransformation under the influence of the cytochrome P_{450} enzyme system with formation of three primary metabolites: 3-hydroxydiclofenac, 4-hydroxydiclofenac, and 5-hydroxydiclofenac. Primary metabolites are conjugated to form two secondary ones - 4,5-dihydroxy-diclofenac and H-hydroxy-4-methoxydiclofenac (3,4-HMD)[9]. All metabolites significantly assign to the primarymedication in therapeutic activity[8]. The half-excretion of Diclofenac Sodium and four of its five major metabolites ranges on average from 1 to 3 hours, but for 3,4-HMDit reaches 80 hours. DS does not cumulate on long-term using, all its metabolites are excreted with urine and bile. 95.7% of the medication is bound with the serum proteins[7]. According to previous research works, the concentration of Diclofenac Sodium reached a maximum after intramuscular injection after 15 and 25 minutes[10]. Besides, it should be noted that most of NSAIDs belong to the category of medications metabolized in the liver, which makes the problem of metabolism studying in the body particularly relevant in practical terms.

Rheumatoid arthritis is often accompanied by visceral manifestations from other organs and systems, as well as concomitant diseases (comorbid state)[11], which can affect pharmacokinetic parameters of used NSAIDs.

The aim of the study is to research in a comparative aspect certain indicators of Diclofenac Sodium pharmacokinetics in patients with rheumatoid arthritis accompanied by gastric microbiocenosis disorder (gastric dysbiosis) and without gastric microbiocenosis disorder (without dysbiosis).

Materials and Method

There were 38 patients with reliably established RA at the age of 18-60 years, with disease duration of more than 5 years. RA patients were divided into 3 groups: RA patients without dysbiosis - 28.6%, RA patients with dysbiosis -42.8%, RA patients with dysbiosis and H.pylori- 28.6%.

For determination of Diclofenac in blood plasma a highly effective liquid chromatography (HELC) was used with mass spectrometry (MS). The Agilent 6420 Ultra Highly Effective Liquid Chromatograph (UHELC) device with triple quadrupole mass spectrometer was used (produced by Agilent Technologies, USA). HELC pure acetonitrile was supplied by Sigma-Aldrich Trading Co. (Schnelldorf, Germany). Ultra-pure water was obtained by a water purification system produced by Sartorius LabInstruments GmbHЄtCo.KG (Goettingen, Germany). All other chemical substances were of analytical purity and were used without further purification.

Preparation of Samples: Control blood samples were taken from the patients after Diclofenac tablets application (50 mg) (positive control) after 0.5, 6 and 12 hours. The blood samples were centrifuged at 2000 rpm during 6 minutes. After these measures the blood plasma was injected into HELC tube for the analysis.

For preparing standard Diclofenac samples, the substrate was dried, then the exact amount was weighed, and a basic water solution was prepared at a concentration of 1 mg/ml. Samples of different Diclofenac concentrations were prepared from this solution for both qualitative and quantitative analysis.

HELC-MS/MS screening: HELC analysis was performed with samples volume 1mcl,which was injected with the help of an automatic sampler. As a

mobile phase only water acidified with 0.01% formic acid or acetonitrile water added 0.01% formic acid for positive ion control at a flow rate of 0.2 ml/min was used.

Analysis were performed by Full Scan Mode (Fullscanmode) for determination of the chemical composition of the substance.

Qualitative and quantitative analysis of Diclofenac Sodium: Standard solutions of Diclofenac were newly prepared by diluting the base solution (1 mg/ml) in ultrafine water. Samples ranging from 0.01 to 1000 ng/µl were prepared for quantitative analysis for calibration, detection limit (DL) and quantitative limit (QL). These solutions were stored at 4ºC before the analysis. DL and QL were determined experimentally from the signal-to-noise ratio by diluting the basic concentration (1 mg/ml)

Results

The results of these studies are shown in Figures 1,2,3: As it can be seen from the Fig.1, in patients with rheumatoid arthritis without gastric dysbiosis, Cel is decreased for 34.4%. compared to the control index. At the same time in patients with rheumatoid arthritis with gastric dysbiosis this indicator is decreased to a greater extent (almost 1.5 times compared to the control). Considering that this indicator of pharmacokinetics reflects the rate of medication excretion from the body, it becomes obvious that in condition of rheumatoid arthritis the rate of medication excretion from the patient ‘s body is slowed down. And in accompaniment ofgastric dysbiosis this process is highly aggravated.

It is generally known that the rate of xenobiotics excretion, including medications metabolizing in the liver,first of all depends on the rate of their biotransformation (metabolism) in the body. In this regard, we studied the Cl indicator, which reflects the degree of body purification from the medication. Analysis of this indicator results also shows a significant inhibition of this body function in rheumatoid arthritis conditions, especially in the presence of comorbid states (Fig. 2).

Inhibition of medicine metabolism in the body and decrease of the rate of their excretion from the body is accompanied by accumulation of the applied medicine in the blood. Indeed, as it can be seen from the data presented in the figure, in patients with rheumatoid arthritis the indicator T1/2 is extended 1.5 times in comparison with the control. And in conditions of gastric dysbiosis, almost 2 times, respectively (Fig. 3).

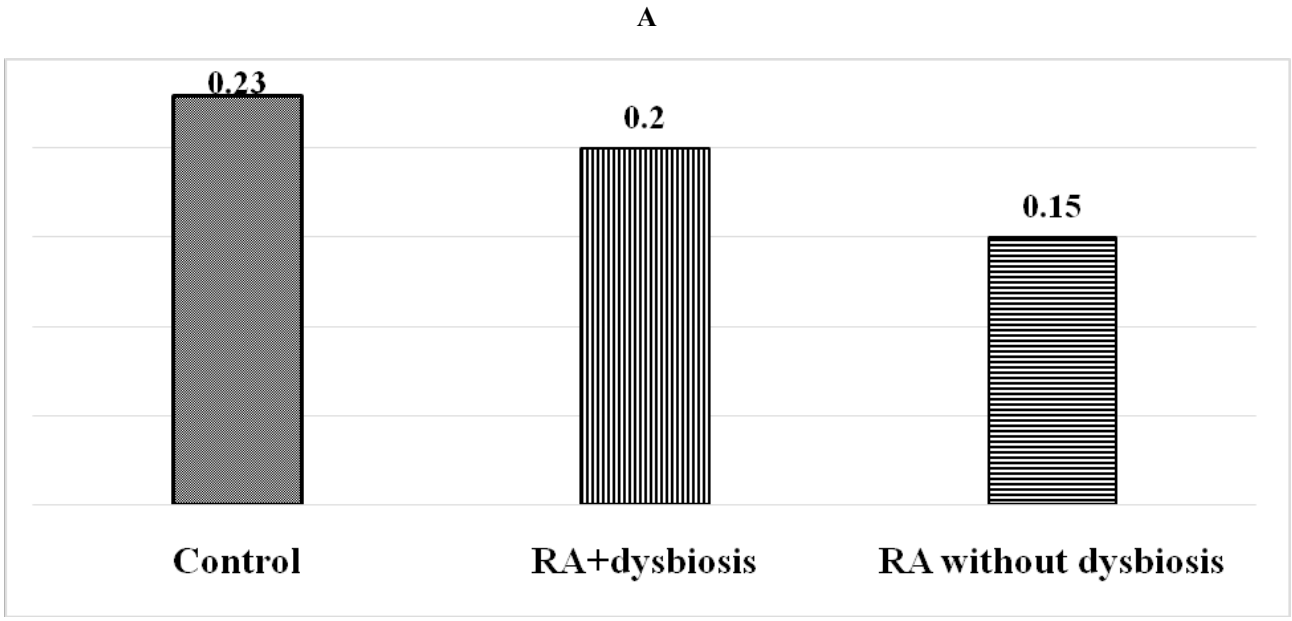


Fig. 1. Indicators of Diclofenac Sodium pharmacokinetics in patients with rheumatoid arthritis: A – indicator ofConstant Elimination (Cel)

B

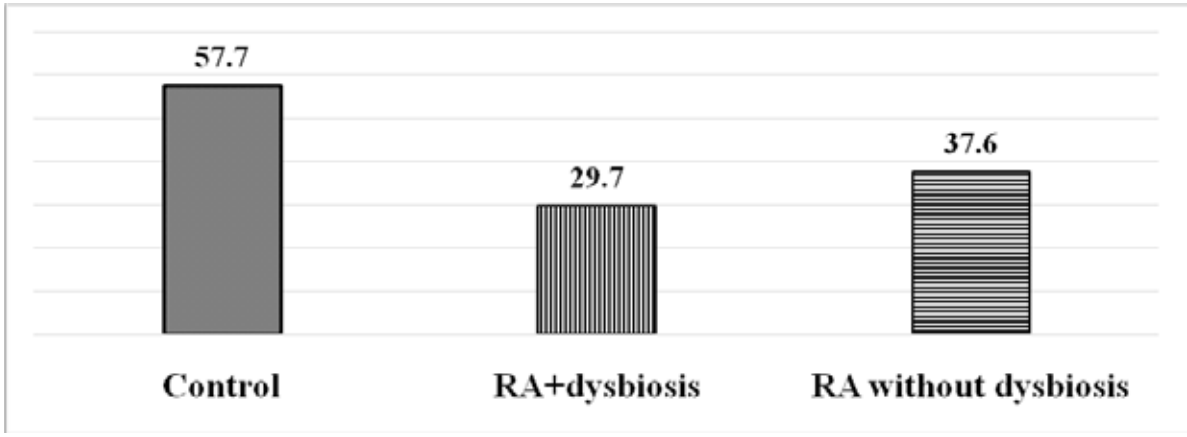


Fig. 2. Indicators of Diclofenac Sodium pharmacokinetics in patients with rheumatoid arthritis: B – clearance of the medication (Cl)

C

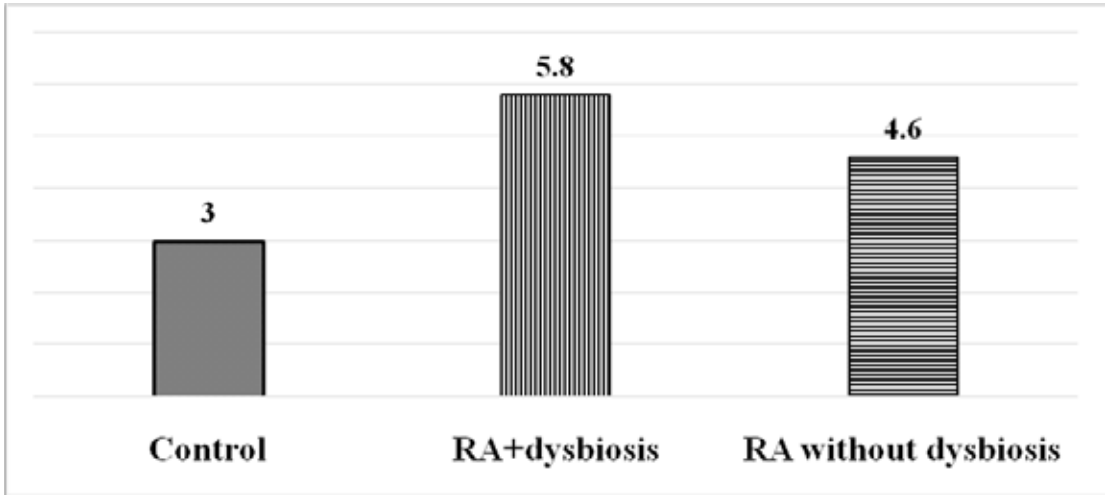
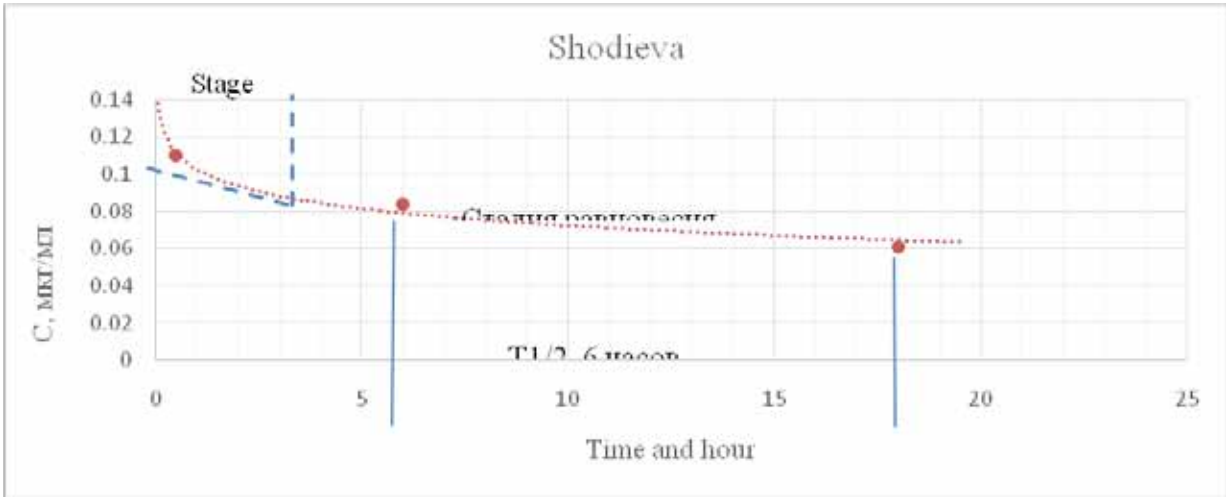


Fig. 3. Indicators of Diclofenac sodium pharmacokinetics in patients with rheumatoid arthritis: C –half-excretion period ($T_{1/2.}$).

The following is the example of calculating of the pharmacokinetic indicators of the patient with RA (Fig. 4)



V_p = Dose/C_0 = 25 mg/0,1 = 250 l

C_{el} = 0,693/$T_{1/2}$ = 0,693/6 hour = 0,1155h^{-1}

Cl = $V_p \times C_{el}$ = 250 l×0,1155h^{-1} = 28,875 l/h

Normally, Diclofenac is excreted in 2-3 hours. Let's assume, if this processtakes 2.5 hours, then

C_{el}(norm) = 0,693/$T_{1/2}$ = 0,693/2,5 hour = 0,2772 h^{-1} **$C_{el} < C_{el}$ (norm)**

Cl(norm) = $V_p \times C_{el}$ = 250 l×0,2772h^{-1} = 69,3 l/h **Cl<Cl (norm)**

Discussion

Therefore, in patients with rheumatoid arthritis there is a significant extension of the half-excretion of the researched medication, and in the condition of comorbid states this indicator grows even greater,that increases the risk of development of side effect.

Considering the results of pharmacokinetics, there are two variants for possible decrease of the NSAID side effects:

1. It is necessary to reduce the NSAID dose without changing the medicine taking intervals; or
2. Without changing the dose, to extend the intervals, i.e. reduce the multiplicity of medication appointment.

Besides, to protect gastric mucosa, it is preferable to add antacids, proton pump inhibitors, M-cholinoblocators and H2-histamine receptor blockers to the general treatment.

Thus, accordingto the above mentioned, we have also studied and analyzed the structure and frequency of side effects of the conducted treatment against the background of NSAID appointment in the examined groups of patients. The results of this analysis are given in the Table 1.

Table 1: Structure and frequency of manifestations of NSAID side effects in patients with rheumatoid arthritis

Lesion of GDZ	Group of patients		
	RA without dysbiosis	RA with dysbiosis	RA with dysbiosisand H. pylori
Heartburn (%)	50	58	80
Burp (%)	18	33	12
Heaviness in epigastrium (%)	12	42	50
Pains in epigastrium (%)	58	54	68
Constipation (%)	-	14	4
Poor appetite (%)	10	15	18
Esofagit (%)	77	50	88
Gastric ulcer and DPC (%)	10	25	28

Conclusion

As itis seen from the presented data above, in the group of patients with rheumatoid arthritis accompanied by gastric dysbiosis, the frequency of occurrence of the most characteristic signs of side effects becomes significantly higher than in the group of patients with rheumatoid arthritis without gastric dysbiosis. At the same time such manifestations as heartburn, heaviness in epigastria, pain in epigastria in the group of patients with rheumatoid arthritis and gastric dysbiosis increase for 38%, 19% and 26%, respectively. They also have a relatively high incidence of esophagitis and gastric and duodenal ulcers.

Therefore, in conditions of rheumatoid arthritis with comorbid states, there is a more frequent occurrence of the NSAID side effects.

Thus, researches conducted and analysis of their results indicate that in conditions of rheumatoid arthritis, particularlyat comorbid states, there are reasonablechanges in the NSAID pharmacokinetics. The decreasingof metabolic rate and the extension of the

NSAID half-excretion increases the risk of side effects, especially on the side of the GIT, which significantly affects the disease course and results of the treatment. This circumstance dictates the need to take these results into account in the treatment of the studied pathology and in the development of a personalized approach to the treatment of rheumatoid arthritis.

Consent: It is not applicable.

Ethical Approval: All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of Interest: Authors declare that there is no any conflict of interest for the results of the study.

Authors' Contributions: This work was carried out in collaboration between all authors. Author NKT designed the study, wrote the protocol, performed data collection, wrote the initial manuscript and revisions. Author MSK, BShA performed the literature review, data analysis and processing, manuscript writing, edition and revisions, author MVS helped with the writing of the manuscript. Author AMM helped with the statistical analysis. Author KLK edited the manuscript and revisions. All authors read and approved the final manuscript.

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