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SOME INDICATORS OF PHARMACOKINETICS OF SODIUM DICLOFENAC IN PATIENTS WITH RHEUMATOID ARTHRITIS TAKING INTO ACCOUNT COMORBIDE CONDITIONS

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ABSTRACT

The aim of the study was to study in a comparative aspect some of the pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis with impaired gastric microbiocenosis (gastric dysbiosis) and without disturbance (without dysbiosis). Material and methods: We examined 38 patients aged 18 to 60 years, with I-II-III degree of disease activity. In addition to general clinical examination conductedenzyme immunoassay and urease test to determine Helicobacter pylori andhigh performance liquid chromatography to determine the pharmacokinetics of diclofenac. Results: studies and analysis of their results indicate that in conditions of rheumatoid arthritis, in particular, in the presence of comorbid conditions, there is a decrease in the metabolic rate and lengthening the half-life of NSAIDs, which increases the risk of side effects, especially from the gastrointestinal tract and significantly affects the course of the disease and treatment results.

KEYWORDS: Rheumatoid arthritis, diclofenac, high performance liquid chromatography, pharmacokinetics.

INTRODUCTION

Currently, much attention is paid to conducting pharmacokinetic (FC) studies to study the processes of drug intake, distribution, biotransformation and excretion, as well as identifying the relationship between the concentration of a drug substance and (or) its metabolites in biological fluids and tissues and the pharmacological effect. Clinical pharmacokinetics determines what dosage of medicinal substances provides their necessary concentration in the body's media to achieve the optimal therapeutic effect. Currently, several methods for determining diclofenac in biological fluids are known: potentiometric analysis,[10] high performance liquid chromatography (HPLC),[3] capillary zone electrophoresis,[7] spectrofluometry,[8] thin layer chromatography,[9] polarographic analysis.[4]

It is well known that in the treatment of rheumatoid arthritis (RA), non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as symptomatic therapy, of which diclofenac sodium (DN) is most often used. The duration of the anti-inflammatory effect, the effectiveness of NSAIDs as a whole are directly dependent on the level of effective concentration of the

drugs and the duration of their circulation in the blood in free form. In clinical practice, these parameters are determined by a number of pharmacokinetic parameters, in particular, Cal (elimination constant), Cl (drug clearance), T1 / 2 (drug half-life), etc. In the human body, diclofenac undergoes biotransformation under the influence of the enzyme system of cytochrome P450 with the formation of three primary metabolites: 3-hydroxydiclofenac, 4-hydroxydiclofenac and 5-hydroxydiclofenac. Primary metabolites are conjugated to form two secondary metabolites - 4,5-dihydroxy-diclofenac and 3-hydroxy-4-methoxydiclofenac (3,4-HMD). All metabolites are significantly inferior to the original drug in therapeutic activity. The half-life of diclofenac sodium and four of its five main metabolites varies on average from 1 to 3 hours, but for 3,4-HMD it reaches 80 hours. DN does not cumulate with prolonged use, all its metabolites are excreted in urine and bile. 95.7% of the drug binds to whey proteins.[1] According to the results of previous studies, the concentration of diclofenac sodium reached a maximum after intramuscular administration after 15 and 25 minutes.[2,5,6] In addition, it should be noted that most NSAIDs belong to the category of drugs metabolized in

the liver, which makes the study of their metabolism 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) [eleven]that can affect the pharmacokinetic parameters of the NSAIDs used.

The purpose of our studies is to study in a comparative aspect of some indicators of the pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis with a violation of gastric microbiocenosis (gastric dysbiosis) and without disturbance of gastric microbiocenosis (without dysbiosis).

MATERIALS AND METHODS

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

To determine diclofenac in blood plasma, the method of high performance liquid chromatography (HPLC) with mass spectrometric (MS) detection was used. We used an Agilent 6420 Ultra High Performance Liquid Chromatograph (HPLC) with a triple quadrupole mass spectrometer from agilenttechnologies (USA). HPLC pure acetonitrile was purchased from Sigma-Aldrich Trading Co. (Schnelldorf, Germany). Ultrapure water was obtained using a water purification system from Sartorius Lab Instruments GmbH. KG (Gottingen, Germany). All other chemicals were of analytical grade and used without further purification.

Sample preparation
Control blood samples were taken from patients after taking diclofenac tablet (50 mg) (positive control) after 0.5, 6 and 12 hours. Blood samples were centrifuged at 2000 rpm for 6 minutes. After this, blood plasma was introduced into an HPLC column for analysis.

To prepare standard samples of diclofenac, the substrate was dried, the exact amount was weighed, and a basic aqueous solution was prepared at a concentration of 1 mg / ml. Samples with different concentrations of diclofenac were prepared from this solution for both qualitative and quantitative analysis.

HPLC-MS / MS screening
HPLC analyzes were carried out with samples of 1 μl, which were introduced using an automatic sampler. As the mobile phase, either only water acidified with 0.01% formic acid or acetonitrile - water added with 0.01% formic acid for positive ion control at a flow rate of 0.2 ml / min were used.

Analyzes were performed in the mode full scan (RPS) (Fullscanmode) to determine the chemical composition of the plant.

Qualitative and quantitative analysis of diclofenac
Diclofenac standard solutions were freshly prepared by diluting a stock solution (1 mg / ml) in ultrapure water. For quantitative analysis, samples were prepared in the range from 0.01 to 1000 ng / μl for calibration, detection limit (PO) and the limit of quantification (FFP). These solutions were stored at + 4 ° C before analysis. PO and PKO were determined experimentally from the signal-to-noise ratio by diluting the basic concentration (1 mg / ml)

RESULTS AND DISCUSSION

The results of these studies are presented in figures 1,2,3. As can be seen from the data presented in Figure 1 in patients with rheumatoid arthritis without dysbiosis in the stomach, Cal was reduced compared with the control indicator by 34.4%. At the same time, in patients with rheumatoid arthritis with gastric dysbiosis, this indicator is reduced to a greater extent (almost 1.5 times compared with the control). Given that this indicator of pharmacokinetics reflects the rate of excretion of the drug from the body, it becomes obvious that in conditions of rheumatoid arthritis, the rate of excretion of the studied drug from the body of a patient slows down. And in conditions of the attachment of dysbiosis in the stomach, this process is even more aggravated.

It is well known that the rate of excretion of xenobiotics, including drugs metabolized in the liver, primarily depends on the rate of their biotransformation (metabolism) in the body. In this regard, we studied the indicator Cl, which reflects the degree of purification of the body from the drug. An analysis of the results of this indicator also indicates a significant suppression of this function of the body in conditions of rheumatoid arthritis, especially in the presence of comorbid conditions (Fig. 2).

Suppression of the metabolism of drugs in the body and a decrease in the rate of their elimination from the body is accompanied by the accumulation of the drug used in the blood. Indeed, as can be seen from the data presented in the figure in patients with rheumatoid arthritis, the T1 / 2 value is 1.5 times longer compared with the control. And in conditions of the appearance of gastric dysbiosis almost 2 times, respectively (Fig. 3).
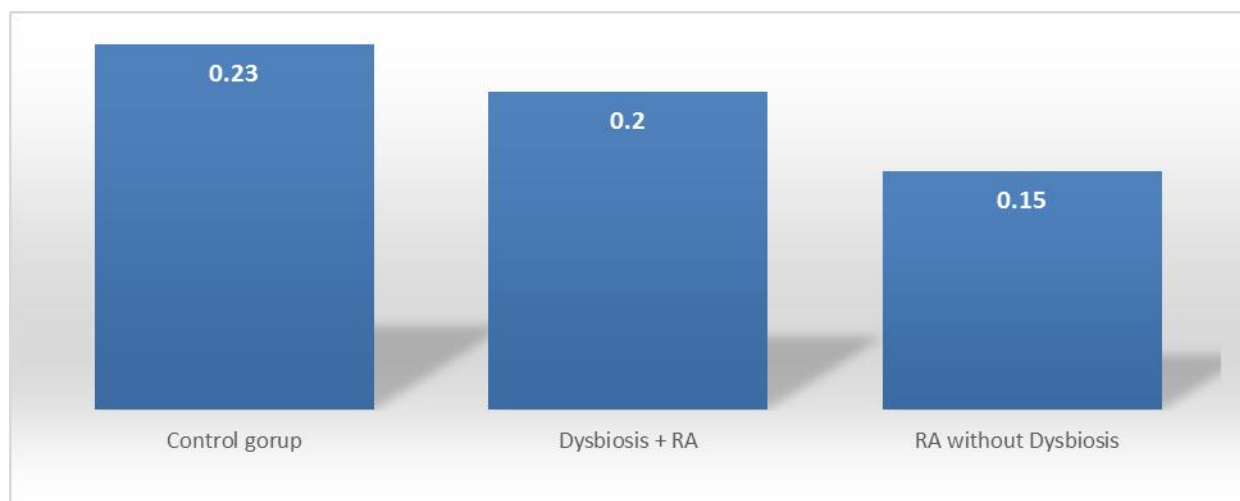
Fig. 1: Pharmacokinetics of sodium diclofenac in patients with rheumatoid arthritis: A - indicator of elimination constant (Cal).
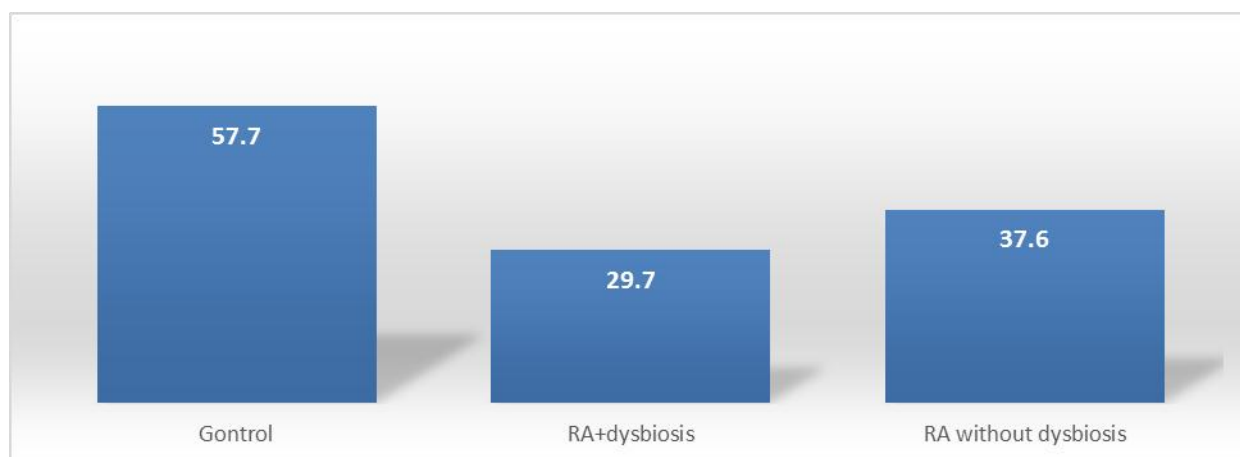

Fig. 2: Pharmacokinetics Diclofenac sodium in patients with rheumatoid arthritis: B-clearance of the drug (Cl).
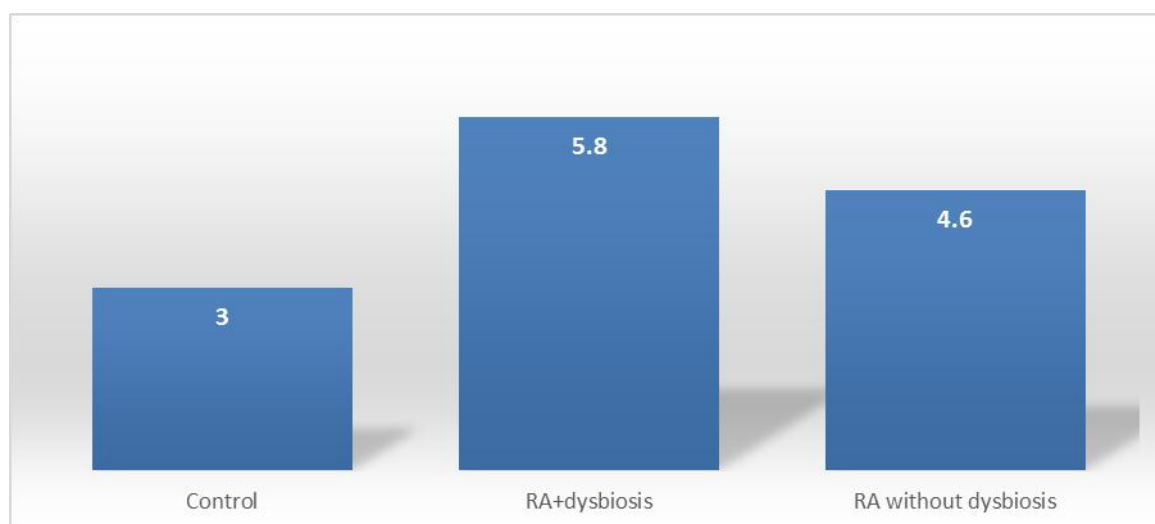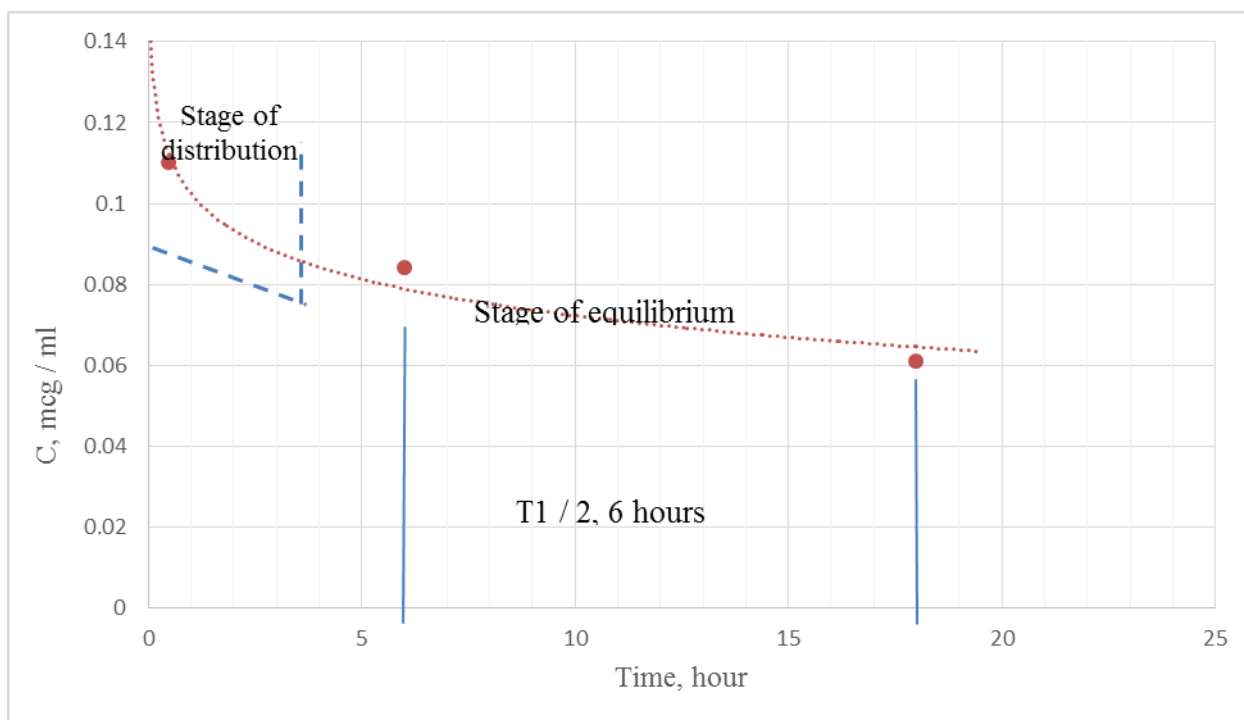

Fig. 3: Pharmacokinetics of Diclofenac sodium in patients with rheumatoid arthritis: B-half-life (T1 / 2.).

The following is an example of calculating the pharmacokinetics of a patient with RA (Fig. 4).

$Vp = Dose / C0 = 25\ mg / 0.1 = 250\ L$
$Kel = 0.693 / T1 / 2 = 0.693 / 6\ hours = 0.1155\ h-1$
$Cl = Vp \times Kel = 250\ L \times 0.1155\ h-1 = 28.875\ L / h$

Normally, diclofenac leaves after 2-3 hours. Suppose if this is 2.5 hours, then

$Kel\ (normal) = 0.693 / T1 / 2 = 0.693 / 2.5\ hours = 0.2772\ h-1\ Kel < Kel\ (normal).$

$Cl\ (normal) = Vp \times Kel = 250\ L \times 0.2772\ h-1 = 69.3\ L / h\ Cl < Cl\ (normal)$

Therefore, in patients with rheumatoid arthritis, a significant lengthening of the half-life of the studied drug is noted, and in the conditions of the addition of comorbid conditions, this indicator is even longer, which increases the risk of side effects.

Given the results of pharmacokinetics to reduce the side effects of NSAIDs, two options are possible:
1) It is necessary to reduce the dose of NSAIDs without changing the intervals of appointment; or
2) Without changing the dose of the drug lengthen the intervals, i.e. reduce the frequency of taking drugs.

In addition, to protect the gastric mucosa, add antacids, proton pump inhibitors, M-anticholinergics and H2-histamine receptor blockers to the treatment.

In connection with the above, we also studied and analyzed the structure and frequency of occurrence of side effects from treatment while taking NSAIDs in the studied groups of patients. The results of this analysis are presented in table 1.

Table 1: The structure and frequency of occurrence of side effects of NSAIDs in patients with rheumatoid arthritis.

GDZ defeat	Patient groups		
	RA without dysbiosis	RA with dysbiosis	RA with dysbiosis and H. pylori
Heartburn (%)	fifty	58	80
Belching (%)	eighteen	33	12
Epigastric severity (%)	12	42	fifty
Epigastric pain (%)	58	54	68
Constipation (%)	-	14	4
Poor appetite (%)	10	fifteen	eighteen
Esophagitis (%)	77	fifty	88
Gastric and duodenal ulcer (%)	10	25	28

As can be seen from the data presented in the group of patients with rheumatoid arthritis with 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. Moreover, such manifestations as heartburn, severity in epigastrium, epigastric pain in the group of patients with rheumatoid arthritis with gastric dysbiosis become more by 38%, by 19% and 26%, respectively. They also have a relatively high incidence of esophagitis and ulcers of the stomach and duodenum.

Therefore, in conditions of rheumatoid arthritis with the presence of comorbid conditions, a more frequent manifestation of the side effect of NSAIDs is observed.

Thus, the studies and analysis of their results indicate that in conditions of rheumatoid arthritis, in particular, in the presence of comorbid conditions, noticeable shifts in the pharmacokinetics of NSAIDs are observed. A decrease in metabolic rate and an increase in the half-life of NSAIDs increases the risk of side effects, especially from the gastrointestinal tract, which significantly affects the course of the disease and treatment outcomes. 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.

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