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# BIOPHARMACEUTICAL ANALYSIS OF THE INTERACTION OF L-THYROXIN, DICLOFENAC SODIUM AND CHONDROITIN SULPHATE, AS COMPONENTS OF PHARMACOTHERAPY OF OSTEOARTHRITIS MANIFESTATIONS RESULTED FROM HYPOTHYROIDISM

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**Ключові слова:** *остеоартроз, гіпотиреоз, L-тироксин, диклофенак натрію, хондроїтину сульфат, біофармацевтична взаємодія*
**Ключевые слова:** *остеоартроз, гипотиреоз, L-тироксин, диклофенак натрия, хондроитина сульфат, биофармацевтическое взаимодействие*

**Abstract. Biopharmaceutical analysis of the interaction of L-thyroxin, diclofenac sodium and chondroitin sulphate, as components of pharmacotherapy of osteoarthritis manifestations resulted from hypothyroidism. Nosivets D.S.** *The article deals with the issue of the biopharmaceutical interaction of L-thyroxin, diclofenac sodium and chondroitin sulfate, as components of pharmacotherapy of osteoarthritis manifestations with concomitant hypothyroidism. It is known that functional insufficiency of the thyroid gland has a negative effect on all types of metabolism and in particular on the condition of the bone and cartilage tissue, leading to the development of osteoarthritis. Existing pharmacotherapeutic approaches to the medical treatment of this pathology require the use of basic hormone replacement therapy, for the correction of thyroid insufficiency, and NSAIDs as drugs for the symptomatic treatment of osteoarthritis. However, to date, questions of the biopharmaceutical interaction of L-thyroxin and diclofenac sodium are not covered, and the prevention of osteoarthritis against the background of hypothyroidism with the help of chondroitin sulfate and its interaction with the components of pharmacotherapy has not been sufficiently studied. Based on the conducted research, it was established that, proceeding from the theoretical analysis of the physicochemical and chemical properties of these drugs, predominantly reversible acid-base interactions are assumed. The probability of strong and irreversible physicochemical reactions is very low and the physical mixtures of these drugs are not subject to negative interactions, which can lead to profound destructive changes on the part of the dosage forms. Since L-thyroxin, diclofenac sodium and chondroitin sulfate are absorbed mainly by simple diffusion, have different transport mechanisms through biological membranes, have different degrees of binding to plasma proteins and various enzyme systems involved in their metabolism and excretion, pharmacokinetic interactions between them are excluded. At the level of pharmacological interaction, the combined and unidirectional effects of the combination of active substances L-thyroxin, diclofenac sodium and chondroitin sulfate are expected, in particular, in degenerative-dystrophic disorders due to functional insufficiency of the thyroid gland, to restore the structure of cartilage and for a complex etiotropic and symptomatic treatment of osteoarthritis and related states.*

**Реферат. Биофармацевтический анализ взаимодействия l-тироксина, диклофенака натрия и хондроитина сульфата как компонентов фармакотерапии проявлений остеоартроза в результате гипотиреоза. Носивец Д.С.** *В статье рассмотрен вопрос биофармацевтического взаимодействия L-тироксина, диклофенака натрия и хондроитина сульфата как компонентов фармакотерапии проявлений остеоартроза при сопутствующем гипотиреозе. Известно, что функциональная недостаточность щитовидной*

*железы негативно сказывается на всех видах обмена веществ и в частности на состоянии костно-хрящевой ткани, приводя к развитию остеоартроза. Существующие фармакотерапевтические подходы медикаментозного лечения данной коморбидной патологии требуют назначения базовой заместительной гормональной терапии, для коррекции недостаточности щитовидной железы, и нестероидных противовоспалительных средств (НПВС), как препаратов симптоматического лечения остеоартроза. Однако на сегодняшний день не освещены вопросы биофармацевтического взаимодействия L-тироксина и диклофенака натрия, а также недостаточно изучена профилактика остеоартроза на фоне гипотиреоза при помощи хондроитина сульфата и его взаимодействие с компонентами фармакотерапии. На основании проведенного исследования установлено, что, исходя из теоретического анализа физико-химических и химических свойств данных лекарственных средств, предполагаются преимущественно обратимые кислотно-щелочные взаимодействия. Вероятность сильных и необратимых физико-химических реакций очень низка, и физические смеси данных лекарственных препаратов не подвергаются негативным взаимодействиям, которые могут привести к глубоким деструктивным изменениям со стороны лекарственных форм. Поскольку L-тироксин, диклофенак натрия и хондроитина сульфат абсорбируются преимущественно путем простой диффузии, имеют различные механизмы транспорта через биологические мембраны, имеют разную степень связывания с белками плазмы крови и различные ферментные системы, вовлеченные в их метаболизм и экскреции, исключаются фармакокинетические взаимодействия между ними. На уровне фармакологического взаимодействия ожидается сочетанное и однонаправленное воздействие комбинации активных веществ L-тироксина, диклофенака натрия и хондроитина сульфата, в частности, при дегенеративно-дистрофических нарушениях вследствие функциональной недостаточности щитовидной железы, для восстановления структуры хрящевой ткани и для комплексного этиотропного и симптоматического лечения остеоартроза и связанных с ним состояний.*

To date, research on comorbid pathology is receiving increasing attention in modern medicine [2]. The urgency of these problems is caused, on the one hand, by the prevalence of the pathology, and on the other - by their mutual aggravating effect, which leads to the emergence of atypical clinical situations [1, 2]. One of these issues is the formation, development and course of osteoarthrosis with insufficient thyroid function [3]. In this comorbid pathological condition simultaneous administration of basic hormone replacement therapy for functional thyroid insufficiency and symptomatic treatment of osteoarthrosis is needed [5, 6]. Also, the issues of prevention of osteoarthritis in concomitant hypothyroidism with the help of symptom-modifying pharmacotherapy have not been solved [4, 9]. Therefore, the question about the study of biopharmaceutical interaction of drugs used in the correction of this pathological condition arises.

The purpose of the work is to conduct biopharmaceutical analysis of the interaction of L-thyroxine, diclofenac sodium and chondroitin sulfate as components of pharmacotherapy for osteoarthritis manifestations against hypothyroidism.

**MATERIALS AND METHODS OF RESEARCH**

In order to evaluate the possible use of three drugs combined – L-thyroxine, diclofenac sodium and chondroitin sulfate, we examined their physicochemical properties, possible chemical reactions they may enter due to the presence of functional groups and pharmacokinetic and pharmacological interactions mainly due to the effect on identical or interconnected biochemical, receptor or functional systems.

**RESULTS AND DISCUSSION**

*An analysis of the physicochemical properties of L-thyroxine* found that L-thyroxine is a derivative of the tyrosine amino acid and is a synthetic analogue of the thyroid hormone - thyroxine. The combination of acid-alkaline properties in one molecule determines the common property of all amino acids to exist in the form of zwitterion (bipolar ion) [10].

Analysis of the acid-alkaline properties of levothyroxine revealed that the dissociation of the carboxyl group occurs already at pH>22.2 (pKa=2.12±0.3), whereas the deprotonation of the amino group - only at pH higher than 7.0 (pKa=6.91±0.25). Due to this, the presence of levothyroxine in the form of zwitterion at physiological pH (in the blood 7.4) is possible. Complete dissociation of phenyl hydroxyl occurs at a much higher pH (pKa=8.94±0.45), but under physiological conditions, levothyroxine mainly exists in the form of a double-charged anion with a protonated amino group [8].

*Analysis of the chemical properties of diclofenac sodium* by functional groups found that diclofenac sodium in its structure is a bifunctional compound containing in its structure a secondary amino group and a carboxyl group in the form of its salt with sodium ion.

An analysis of the alkaline properties of diclofenac sodium showed that the molecule contains an ionized carboxyl group and can exist in two protolytic forms in the aqueous medium. Due to the low value of the constant of ionization, under physiological conditions diclofenac sodium is in the ionized form, which is to a large extent soluble in water.

*An analysis of the physicochemical properties of chondroitin sulfate* showed that chondroitin-4 sulfate is a polymer compound, the elemental link chain of which is the structure of sulfated glucosamine.

Based on the theoretical analysis of the physicochemical and chemical properties of L-thyroxine, diclofenac sodium and chondroitin-4 sulfate, we can assume the possibility of mainly reverse acid-base interactions, which eliminates the possibility of interaction of L-thyroxine (levothyroxine), diclofenac sodium sulphate at the pharmaceutical level.

*Analysis of the possible interactions of compounds at the biological level* revealed that at the stage of intestinal absorption the compounds analyzed use simple diffusion. So, chondroitin-4 sulfate as a component of cartilages and connective tissue, exists in the form of a polymer and is subjected to partial hydrolysis with the release of chondroitin-4 sulfate. Diclofenac sodium, as an exogenous compound, also enters the intestinal wall by simple diffusion. L-thyroxine, despite its similarity to the endogenous compound, is also absorbed by active transport. Therefore, at the stage of intestinal absorption the interaction between these compounds is almost exclusive.

With the blood flow, the compounds enter the liver, where their biotransformation can occur. The bioavailability indicators show that these compounds are biotransformed to varying degrees, so it is necessary to analyze the possibility of their interaction at this stage. However, the enzymes and biotransformation systems involved in the metabolism of each of the compounds are different, lack specificity and have high activity in the body, so no interaction at the metabolic level is expected for this combination of compounds [7].

The distribution of compounds between organs and tissues can also be a passive process, the direction of which is determined by the physicochemical properties of the substances, or active, if active carriers are involved therein. The lack of possible interaction between them is also confirmed by the different degree of binding to plasma proteins. This also results in different half-elimination time - more water-soluble compounds, which may subsequently form glucuronic or sulfate conjugates, have a shorter half-elimination time than high lipophilic L-thyroxine.

The excretion of these compounds and their metabolites is mainly with urine and, in the form of conjugates – partly with feces. Since no specific and unique transport systems have been identified for any of the compounds, it should be concluded that their excretion occurs by means of independent processes and their impact on the others is not expected.

Interaction at the level of biological response is the final and most important stage in drug co-use. The combined use of several active compounds can reduce their dose, reducing the risk of side effects and toxic effects in overdose. Therefore, pharmacodynamic interaction analysis is one of the essentials when assessing the possibility of using a combination of drugs.

According to information on biological targets of these compounds, they have slightly different directions of biological action and, accordingly, the target pharmacological effect. Thus, diclofenac sodium is a classic inhibitor of type II cyclooxygenase (COX-2) and due to inhibition of the activity of this enzyme and reduction of prostaglandin synthesis (mediators of pain and inflammation) it has predominantly analgesic and anti-inflammatory action, L-thyroxine in low dosage accelerats metabolism of lipids, carbohydrates and proteins, and chondroitin sulfate acts mainly as a chondroprotector. However, recent studies have also shown the involvement of chondroitin in the inhibition of NO synthase and metal enzymes, involved in the development of inflammation, osteoarthritis and other diseases.

Thus, at the level of pharmacological interaction one can expect combined and unidirectional effect of the combination of active substances - L-thyroxine, diclofenac sodium and chondroitin sulfate, particularly in degenerative-dystrophic disorders due to functional deficiency of the thyroid gland, in renewal of cartilaginous tissue structure and in the complex etiological and symptomatic treatment of osteoarthrosis and associated conditions.

**CONCLUSIONS**

1. Based on the theoretical analysis of the physicochemical and chemical properties of L-thyroxine, diclofenac sodium and chondroitin sulfate, it is possible to assume the possibility of mainly reverse acid-base interactions. The likelihood of other, strong and irreversible reactions is very low and under normal conditions physical mixtures of these compounds are not expected to be susceptible to interactions that will lead to profound destructive changes.
2. Because L-thyroxine, diclofenac sodium and chondroitin sulfate are mainly absorbed by simple diffusion, have different mechanisms of transport through biological membranes (or those which are not saturated due to their large amount), different degrees of binding to blood plasma proteins and various enzymatic systems involved in their metabolism and excretion one can exclude pharmacokinetic interactions between them.

3. At the level of pharmacological interaction one can expect combined and unidirectional effect of combination of active substances – L-thyroxine, diclofenac sodium and chondroitin sulfate, particularly in degenerative-dystrophic disorders due to functional deficiency of the thyroid gland, in renewal of cartilaginous tissue structure and in the complex etiological and symptomatic treatment of osteoarthrosis and associated states.

Prospects for further development. The work was performed on the basis of the research materials of the Department of Pharmacology and Clinical Pharmacology of the SE "DMA of Health Ministry of Ukraine" on the subject "Pharmacological analysis of organ- and endothelial protection in the conditions of experimental pathological conditions" (State registration N 0118U006631). It is planned to further investigate the effects of nonsteroidal anti-inflammatory drugs and chondroprotectors on the manifestations of osteoarthrosis with concomitant hypothyroidism.

Conflict of interests. The author declares that there is no conflict of interest.

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