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EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND PARACETAMOL ON THE FUNCTIONAL STATE OF THE THYROID GLAND IN EXPERIMENTAL OSTEOARTHRITIS WITH HYPOTHYROIDISM*

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One of the problems in the treatment of comorbid conditions is related to the identification of factors that could predict the effectiveness of treatment of osteoarthritis on the background of hypothyroidism. It is currently known that hypothyroidism (thyroid) leads to metabolic disorders that adversely affect the condition of bone and cartilage tissue, causing the development of osteoarthritis, but the impact of analgesic therapy on the thyroid gland is insufficiently studied [1-5].

This question arises due to the existence of conflicting studies on the various effects of drugs, including non-steroidal anti-inflammatory drugs (NSAIDs) on thyroid hormones in the serum. It is known that drugs can affect the hormonal activity of the thyroid gland in various ways, including through the induction of cytochromes, direct influence on the synthesis and secretion of hormones or their metabolism, clearance, and uptake by tissues, antagonism with transport proteins.

According to Koizumi Y. et al. (2006), mefenamic acid displaces triiodothyronine (T3) and thyroxine (T4) from binding to a transport protein, making more T4 and T3 hormones available to peripheral tissues for thyroid stimulating hormone (TSH) secretion, degradation, and regulation [6]. Also known is the work of Sauvé F. et al. (2003), which states that the administration of meloxicam, carprofen, glucosamine and chondroitin sulfate does not affect the thyroid function of the dog [7].

In a study by Panciera D.L. et al. (2006) studied the effect of deracoxib and aspirin and found that aspirin significantly reduced the mean serum T4 and T3 concentrations, but that deracoxib did not affect serum thyroid hormone levels in any way [8].

The aim of the study was to investigate the effect of NSAIDs and paracetamol on the functional state of the thyroid gland under conditions of experimental osteoarthritis on the background of hypothyroidism.

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MATERIALS AND METHODS

The study was performed on 80 white nonlinear rats weighing 200-250 g, which were kept under standard conditions of the vivarium of the Dnipro State Medical University. Experimental studies have been carried out in accordance with the «General ethical principles of animal experimentation» (Ukraine, 2001), «Bioethical examination of preclinical and other animal research» (Kyiv, 2006) and the provisions of the «European convention for the protection of vertebrate animals used for experimental and other scientific purposes» (Strasbourg, 1986). When conducting the research, the regulation was approved by the ethics committee of the Dnipro State Medical University (protocol number 5 — 02.09.2020).

Experimental osteoarthritis (EOA) was reproduced at the beginning of the study by administering 0,1 ml of monoiodoacetic acid solution (Iodoacetic acid reagent ≥ 98.0% T, No. I4386, manufactured by Sigma-Aldrich Chemie GmbH, Germany) to the knee joint. Monoiodoacetic acid solution was prepared at the rate of 3 mg per 50 μL of sterile saline solution, and the solution was injected once on the first day of the experiment [9, 10] and from the same day began the formation of experimental hypothyroidism (EH) by enteral administration of 0,02% solution of carbimazole (drug «Espacarb», production of Esparma GmbH, Germany; in tablets 5 mg or 10 mg), which was prepared at the rate of 5 mg per 250 ml of saline solution and given with the animals' diet for 6 weeks. The freshly prepared solution was administered to the drinking diet of experimental animals for 6 weeks (42 days) [11].

The 42 days of the experiment reflect the end of the formation of the model of EH and the full development of the model of EOA. Verification of adequate performance of the EOA model in rats was performed using electron microscopy of tissue complexes of the knee joints and changes in the relevant biochemical markers of blood serum [1, 12–14].

Verification of adequate performance of the experimental model of EH was confirmed by the level of TSH, T3, and T4 serum of laboratory animals.

To address the question of the effect of NSAIDs and paracetamol on the functional state of the thyroid gland, which was determined by the level of TSH, T3 and T4 hormones, each of the studied drugs was administered in two doses. The first group of doses is those that were used in the previous stages of the study and corresponded to the average effective doses in terms of analgesic activity and were borrowed from the literature and used repeatedly in preclinical studies. Doses were selected on the basis of calculation based on average and maximum human doses using the coefficient of species sensitivity, and taking into account literature data [15–17].

The second dose group was determined by gradually increasing the first dose group to determine changes in the levels of test hormones in the serum of rats. These doses were also selected on the basis of calculation based on average and maximum human doses using the coefficient of species sensitivity, and taking into account the literature [15–17].

Interpretation of the obtained results was based on the known fact that clinical laboratory diagnosis of hypothyroidism is characterized by an increase in TSH concentration and a decrease in free T4 content, while the concentration of free T3 remains within normal limits or sometimes decreases [18].

By random sampling, rats were divided into experimental groups of 10 animals, which were administered intragastrically for 5 days (from 42 days from the beginning of the experiment) with the studied drugs in the following doses: group - passive control (intact rats — IR); Group I — EOA + EH «without treatment»; Group II — EOA + EH + diclofenac sodium (10; 12 mg/kg); Group III — EOA + EH + ibuprofen (5; 7 mg/kg); Group IV — EOA + EH + meloxicam (10; 12 mg/kg); Group V — EOA + EH + nimesulide (80; 100 mg/kg) [19, 20]; Group VI — EOA + EH + celecoxib (50; 60 mg/kg) [21, 22]; Group VII — EOA + EH + paracetamol (150; 300 mg/kg) [23–26]. Tween-80 solution (Polysorbate 80, Ukraine) was used to obtain a homogeneous suspension by intragastric administration of tablet forms of drugs [16, 17].

The quantitative level of thyroid stimulating hormone (TSH), T3 (triiodothyronine) and T4 (thyroxine) in serum was performed by spe-

cific kits which are based on ELISA (enzyme-linked immunosorbent assay) in vitro twice (on 42 and 47 days of the experiment) using the hormone immunoassay system «Elabscience, Inc.» (USA) according to the method of the manufacturer, which was described in the technical documentation. Standard curves for TSH, T3 and T4 were generated by using reference hormones concentrations supplied by the manufacturer. The sensitivity of this kits for TSH is 0,75 ng/ml, for T3 and T4 — 0,94 pg/ml. The detection range of kit for TSH is 1,25 — 80 ng/ml. The detection ranges of kits for T3 and T4 were 1,56 — 100 pg/ml.

For the reference level of TSH, T3 and T4 adopted the values obtained in intact rats (n=10) (Tab. 1, 2). The blood samples were obtained from the tail vein of the rats by means of puncture using a vacuum system on 42 and 47 days of the experiment [16, 17].

The duration of administration of the drugs was 5 days and by the 47th day of the experiment all animals after the collection of biological material were removed from the study by decapitation under general anesthesia [16, 17].

Statistical differences were performed using the STATISTICA 6.1 software package (Stat SoftInc., Serial number AGAR909E415822FA) and included calculations of arithmetic mean values (M) and their errors (±m). The probability of difference of arithmetic mean (p) values was determined using nonparametric — Mann–Whitney U-test. Probabilities of intragroup and between groups differences were determined using Student's parametric t-test and ANOVA. The differences were considered statistically

Table 1

The level of T3, T4 and TSH of serum in rats on the background of intragastric administration of therapeutic doses of drugs under conditions of comorbid pathology

Group, drug and dose	Initial state (IS) (42 day)			The level of thyroid hormones at 47 day (5 days after drug administration)		
	TSH, ng/ml	T3, pg/ml	T4, pg/ml	TSH, ng/ml	T3, pg/ml	T4, pg/ml
Intact rats (IR) (n=10)	12,34 ± 3,77	28,1 ± 3,54	23,4 ± 2,97	11,7 ± 3,56	26,7 ± 3,67	23,7 ± 3,73
Group I — EOA + EH «without treatment» (n = 10)	64,8* ± 13,59	27,1 ± 3,29	8,7* ± 3,35	65,2* ± 3,51	27,7 ± 3,35	8,6* ± 2,88
Group II — EOA + EH + diclofenac sodium (D) 10 mg/kg (n = 10)	65,14 ± 12,59	28,2 ± 3,83	8,1 ± 2,79	65,3 ± 3,80	27,6 ± 2,88	8,4 ± 2,41
Group III — EOA + EH + ibuprofen (I) 5 mg/kg (n = 10)	66,0 ± 3,81	27,3 ± 3,80	7,4 ± 2,30	65,0 ± 3,54	26,5 ± 3,61	7,7 ± 2,39
Group IV — EOA + EH + meloxicam (Mel) 10 mg/kg (n = 10)	64,2 ± 3,27	26,4 ± 3,97	8,4 ± 2,70	64,5 ± 3,43	28,4 ± 3,36	9,1 ± 3,25
Group V — EOA + EH + nimesulide (N) 80 mg/kg (n = 10)	64,7 ± 3,35	30,0 ± 3,16	9,1 ± 3,44	64,5 ± 3,20	28,6 ± 3,36	7,8 ± 2,68
Group VI — EOA + EH + celecoxib (C) 50 mg/kg (n = 10)	64,1 ± 3,32	26,9 ± 3,85	7,2 ± 2,59	65,2 ± 3,49	29,4 ± 3,05	8,3 ± 3,49
Group VII — EOA + EH + paracetamol (P) 150 mg/kg (n = 10)	65,3 ± 3,38	26,6 ± 3,91	7,8 ± 2,39	66,1 ± 3,78	26,1 ± 3,51	8,5 ± 3,54

Note:

* $p < 0.05$ in relation to the indicators in the groups.

Table 2

The level of T3, T4 and TSH of serum in rats on the background of intragastric administration of higher therapeutic doses of drugs under conditions of comorbid pathology

Group, drug and dose	Initial state (IS) (42 day)			The level of thyroid hormones at 47 day (5 days after drug administration)		
	TSH, ng/ml	T3, pg/ml	T4, pg/ml	TSH, ng/ml	T3, pg/ml	T4, pg/ml
Intact rats (IR) (n = 10)	12,34 ± 3,77	28,1 ± 3,54	23,4 ± 2,97	11,7 ± 3,56	26,7 ± 3,67	23,7 ± 3,73
Group I — EOA + EH «without treatment» (n = 10)	64,8¤ ± 13,59	27,1 ± 3,29	8,7¤ ± 3,35	65,2 ± 3,51	27,7 ± 3,35	8,6 ± 2,88
Group II — EOA + EH + diclofenac sodium (D) 12 mg/kg (n = 10)	65,14¤ ± 12,59	28,2 ± 3,83	8,1¤ ± 2,79	56,1 ± 3,25	30,9 ± 3,68	9,3 ± 2,77
Group III — EOA + EH + ibuprofen (I) 7 mg/kg (n = 10)	66,0¤ ± 3,81	27,3 ± 3,80	7,4¤ ± 2,30	44,7#* ± 3,56	30,6 ± 3,85	9,1#* ± 3,40
Group IV — EOA + EH + meloxicam (Mel) 12 mg/kg (n = 10)	64,2¤ ± 3,27	26,4 ± 3,97	8,4¤ ± 2,70	49,7#* ± 3,53	28,1 ± 3,51	10,7#* ± 3,15
Group V — EOA + EH + nimesulide (N) 100 mg/kg (n = 10)	64,7¤ ± 3,35	30,0 ± 3,16	9,1¤ ± 3,44	46,3#* ± 3,49	34,4 ± 3,65	11,5#* ± 3,35
Group VI — EOA + EH + celecoxib (C) 60 mg/kg (n = 10)	64,1¤ ± 3,32	26,9 ± 3,85	7,2¤ ± 2,59	55,7 ± 3,23	29,4 ± 3,85	8,2 ± 2,86
Group VII — EOA + EH + paracetamol (P) 300 mg/kg (n = 10)	65,3¤ ± 3,38	26,6 ± 3,91	7,8¤ ± 2,39	66,4 ± 3,51	27,1 ± 3,71	8,1 ± 3,21

Note:

\# $p < 0,05$ in relation to the corresponding indicator in the initial state (IS) (42 days),

* $p < 0,05$ in comparison with the indicators of the active control group (Group I EOA + EH — «without treatment»),

¤ $p < 0,05$ in comparison with the indicators of the group of IS passive control (intact rats — IR).

significant at $p \leq 0.05$. Before applying the parametric criteria, the hypothesis of a normal law of distribution of random variables was tested [27].

RESULTS AND THEIR DISCUSSION

The choice of a wide range of doses is due to the fact that in the available literature we found data on the effect of some NSAIDs on the functional state of the thyroid gland at high therapeutic doses, but the studies were isolated [6–8]. The results are presented in Table 1 and Table 2.

As can be seen from Table 1, on the 47th day of the experiment in all groups of experimental animals formed thyroid insufficiency. Thus, on 42 days in Group I (rats with EOA + EH «without treatment») there was a decrease in T4 by 2,69 times ($p < 0,05$) and an increase in TSH by 5,25 times ($p < 0,05$), compared with intact rats by 42 days (completion of the formation of experimental models). This condition persists without significant differences on the 47th day of the experiment, which indicates the adequacy of the performed model of experimental hypothyroidism.

After 5 days of administration of diclofenac sodium (10 mg/kg), paracetamol (150 mg/kg), nimesulide (80 mg/kg) and celecoxib (50 mg/kg) on 47 day of the experiment, no significant differences were observed in the effect on thyroid hormone levels in rat serum compared to with animals of Group I (EOA + EH "without treatment"). As the data of Table 1, the dynamics of hormone levels had only a tendency to decrease, which did not reach statistically significant values ($p > 0,05$).

Higher therapeutic doses of drugs under the conditions of simulation of EOA and hypothyroidism are presented in Table 2.

As can be seen from Table 2, the administration of the studied drugs was accompanied by a multidirectional effect on the content of hormones T3, T4, and TSH in rats with comorbid pathology.

In particular, diclofenac sodium (12 mg/kg), celecoxib (60 mg/kg), and paracetamol (300 mg/kg) when administered intragastrically did not cause significant changes in thyroid hormones (T3 and T4) and TSH in the serum of rats with comorbid pathology. In contrast, drugs such as ibuprofen (7 mg/kg) (Group III), meloxicam (12 mg/kg) (Group IV) and nimesulide (100 mg/kg) (Group VI) were likely to reduce serum TSH levels in rats with EOA + EH in 1,47; 1,3 and 1,4 times respectively. Against their background, at the same time, there was a significant increase in T4 levels by 1,23; 1,27, and 1,26 times respectively.

Thus, the results showed that the serum levels of thyroid hormones T3, T4, and TSH in rats depend on the dose of the drug under study and the drug itself.

Thus, when prescribing medium therapeutic doses of drugs studied in the simulation of osteoarthritis and hypothyroidism, no significant differences in the effect on hormone levels in the serum of rats were observed ($p > 0,05$).

Increasing the doses of the studied drugs within the therapeutic range revealed a multidirectional effect on the levels of TSH, T3, and T4 in the serum of rats. Drugs were conditionally divided into 2 groups: those that adversely affected the level of thyroid hormones and TSH (ibuprofen, meloxicam, nimesulide) and those that did not significantly affect the altered hormonal background in comorbid pathology (diclofenac sodium, celecoxib, paracetamol).

CONCLUSIONS

1. Analgesics have a variety of effects on thyroid function in comorbid conditions (experimental osteoarthritis and hypothyroidism), which depends on both the drug itself and its dose.
2. Identified drugs that can dose-negatively affect the concentration of hormones. Thus, ibuprofen (7 mg/kg), meloxicam (12 mg/kg) and nimesulide (100 mg/kg) decreased TSH levels and increased serum T4 levels, which exacerbated hypothyroidism.
3. In the pharmacotherapy of osteoarthritis on the background of hypothyroidism, it is necessary to take into account the effect of analgesics on the hormones TSH, T3, and T4, which should be borne in mind when correcting the functional activity of the thyroid gland.

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EFFECT OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND PARACETAMOL ON THE FUNCTIONAL STATE OF THE THYROID GLAND IN EXPERIMENTAL OSTEOARTHRITIS WITH HYPOTHYROIDISM

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The question of the effect of NSAIDs on the functional state of the thyroid gland arises due to the existence of conflicting studies on the various effects of drugs, in particular NSAIDs on thyroid hormones in the serum. It is known that drugs can affect the hormonal activity of the thyroid gland in various ways, in particular through the induction of cytochromes, direct influence on the synthesis and secretion of hormones or their metabolism, clearance and uptake by tissues, antagonism with transport proteins. **The aim** of the study was to investigate the effects of NSAIDs and paracetamol on the functional state of the thyroid gland in osteoarthritis with hypothyroidism.

The study was performed on 80 nonlinear white rats with reconstituted osteoarthritis and hypothyroidism. To address the question posed about the effect of NSAIDs and paracetamol on the functional state of the thyroid gland, which was determined by the level of hormones TSH, T3 and T4, each of the studied drugs was administered in two doses. Doses were chosen based on calculations based on average and maximum human doses, using a species sensitivity factor, and taking into account data from the literature. Interpretation of the results obtained was based on the known fact that clinical laboratory diagnosis of hypothyroidism is characterized by increased concentration of TSH and decreased content of free T4, while the concentration of free T3 remains within the normal range or sometimes decreases.

The conducted study revealed that analgesic drugs exhibit a variety of effects on thyroid function in conditions of comorbid pathology, which depends on both the drug itself and its dose.

The authors have identified drugs that can adversely affect hormone concentration in a dose-dependent manner. Thus, ibuprofen (7 mg/kg), meloxicam (12 mg/kg) and nimesulide (100 mg/kg) reduced the TSH level and increased the serum T4 level in rats, which aggravated hypothyroidism. It was proved that pharmacotherapy of osteoarthritis against the background of hypothyroidism should take into account the effect of analgesics on the hormones of TSH, T3 and T4, which should be kept in mind while correcting the functional activity of the thyroid gland.

Keywords: osteoarthritis, hypothyroidism, non-steroidal anti-inflammatory drugs, pharmacotherapy, thyroid stimulating hormone, triiodothyronine, thyroxine.

ВПЛИВ НЕСТЕРОЇДНИХ ПРОТИЗАПАЛЬНИХ ЗАСОБІВ ТА ПАРАЦЕТАМОЛУ НА ФУНКЦІОНАЛЬНИЙ СТАН ЩИТОПОДІБНОЇ ЗАЛОЗИ ПРИ ОСТЕОАРТРОЗІ НА ТЛІ ГІПОТИРЕОЗУ

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Питання впливу нестероїдних протизапальних засобів (НПЗЗ) на функціональний стан щитоподібної залози постає внаслідок існування суперечливих досліджень про різний вплив лікарських засобів, зокрема НПЗЗ на гормони щитоподібної залози у сироватці крові. Відомо, що лікарські засоби можуть впливати на гормональну активність щитоподібної залози різними шляхами, зокрема через індукцію цитохромів, безпосередній вплив на синтез та виділення гормонів або їх метаболізм, кліренс та поглинання тканинами, антагонізм з транспортними білками. **Мета роботи** полягала в дослідженні питання впливу НПЗЗ та парацетамолу на функціональний стан щитоподібної залози при остеоартрозі на тлі гіпотиреозу.

Дослідження проведенні на 80 білих нелінійних щурах, яким відтворений остеоартроз та гіпотиреоз. Для вирішення встановленого запитання про вплив НПЗЗ та парацетамолу на функціональний стан щитоподібної залози, який визначали за рівнями тиреотропного гормону (ТТГ), трийодтироніну (Т3), та тироксину (Т4), кожний з досліджуваних препаратів вводили в двох дозах. Дози були вибрані на основі розрахунку виходячи з середніх та максимальних доз людини із використанням коефіцієнту видової чутливості, та з урахуванням даних літератури. Інтерпретація отриманих результатів засновувалась на відомому факті, що клінічна лабораторна діагностика гіпотиреозу характеризується підвищенням концентрації ТТГ та зниженням вмісту вільного Т4, в той самий час коли концентрація вільного Т3 залишається в межах норми або іноді знижується.

Проведене дослідження дозволило встановити, що знеболюючі препарати проявляють різноманітний вплив на функцію щитоподібної залози в умовах коморбідної патології, що залежить як від самого препарату, так і його дози.

Авторами визначені препарати, які здатні дозозалежно негативно впливати на концентрацію гормонів. Так, ібупрофен (7 мг/кг), мелоксикам (12 мг/кг) та німесулід (100 мг/кг) знижували рівень ТТГ та підвищували рівень Т4 у сироватці крові щурів , що посилювало стан гіпотиреозу.

Доведено, що при фармакотерапії остеоартрозу на тлі гіпотиреозу необхідно враховувати вплив аналгетиків на гормони ТТГ, Т3 та Т4, що треба мати на увазі при корекції функціональної активності щитоподібної залози.

Ключові слова: остеоартроз, гіпотиреоз, нестероїдні протизапальні засоби, фармакотерапія, тиреотропний гормон, трийодтиронін, тироксин.