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EFFECT OF DICLOFENAC SODIUM ON MECHANISMS OF DIFFERENTIATION OF BONE MARROW CELLS AND PERIPHERAL BLOOD: A LITERATURE REVIEW

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Кровотворна система являє собою популяцію багатьох клітин які виконують в організмі певні функції. Фармацевтична промисловість створює нові препарати з групи не стероїдних протизапальних засобів, але «золотим» стандартом залишається препарат «Диклофенак натрію». При деяких станах людина вимушена приймати цей препарат впродовж тривалого часу, а подекуди пожиттєво. Залишається невстановленим механізм впливу препарату на клітини кісткового мозку за умови тривалого використання. В ході аналізу літератури встановлено, що при вживанні препарату проявляє себе токсична дія на клітини крові та органів кровотворення. Поступово токсична дія зменшується, але тривала дія препарату на організм щура сприяє пригніченню розвитку еритроцитарного та мієлоцитарного ростків кісткового мозку. Оптимальним для використання є період до 10 днів, а потім слід шукати більш безпечніший для організму препарат.

Ключові слова: кістковий мозок, Диклофенак натрію, еритроцити, мієлоцити, токсична дія.

The hematopoietic system is a population of many cells that perform certain functions in the body. The pharmaceutical industry creates new drugs from the group of nonsteroidal anti-inflammatory drugs, but the "gold" standard remains the drug Diclofenac Sodium. In some conditions, a person is forced to take the drug for a long time, and sometimes all life. The mechanism of the drug effect on the bone marrow cells under the condition of long-term administration remains unclear. In the process of analyzing the literature, it has been established that the use of the drug has a toxic effect on the blood cells and blood-forming organs. Gradually, the toxic effect is reduced, but the long-term effect of the drug on the rat organism contributes to the inhibition of the development of erythrocyte and myelocytic sprouts of the bone marrow. A period of up to 10 days is optimal for use, and then it is worthwhile to look for a drug that is safer for the body.

Keywords: bone marrow, Diclofenac Sodium, erythrocytes, myelocytes, toxic effect.

The hematopoietic system is a set of populations of various cells that perform highly specialized functions and have a limited life cycle. In humans, hemopoiesis begins in the early embryonic period. In this connection, the embryonic hemopoietic organs (yolk sac, fetal liver, thymus, spleen, lymph nodes and bone marrow) and the organs of hematopoiesis that function after birth [1, 2] are isolated.

Rapid development of pharmaceutical industry creates conditions for the global use of NSAIDs. The main pharmaceutical drug that has been widespread in medical practice is Diclofenac Sodium. The molecule was synthesized by A. Sallmann and R. Pfister in the form of sodium salt and was introduced into clinical practice in 1973. Diclofenac is characterized by partial solubility in hydrophilic and hydrophobic environments, has a short half-life and is rapidly absorbed with oral administration [3]. It is widely used in surgery, traumatology, sports medicine (with damage to the musculoskeletal system, soft tissues, for the purpose of pain relief after surgical intervention); for the treatment of back pain syndrome, tunnel syndromes, migraines - in neurology: for the treatment of dysmenorrhea, adnexitis - in obstetric and gynecological practice. It has WHO's top recommendations for the treatment of cancer patients and has been used by patients for many years [4]. In the last decade, a new class of NSAIDs, the so-called specific (highly selective) cyclooxygenase-2 inhibitors (COX), is being actively improved and developed, with lower toxicity compared to standard NSAIDs [5].

Under conditions of increased pharmaceutical chemical loading on a patient, the most important task of medical science is to assess the homeostatic function of the body in the pre-nosological definition and diagnosis of the effects of NSAIDs.

Actual and interesting in the study of the cerebrospinal fluid of experimental animals are the chemical and pharmacological properties of Diclofenac Sodium, which refer to it for weak organic acids and evidently affect the immunity of the organism, causing a refractory phase

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within 2-3 days [6,7]. In literary sources, the questions of immunomodulatory properties of Diclofenac Sodium, which result in faster suppression of all inflammatory processes, are widely discussed [8,10].

In this regard, it is important to study the mechanisms of forming the effect of the drug on the system of hematopoiesis, which underlies the development of pathological phenomena. It is essential to develop the nosological correlates for estimation of the homeostatic function of the organism under the conditions of the action of Diclofenac Sodium. Also, the need to study the state of the system ofhematopoiesis is dictated, first of all, by its importance in maintaining the constancy of the internal environment of the organism and the risk of occurrence of pathological phenomena in case of its disrupted functioning. In recent years, the study of the state of bone marrow as a target for toxic effects of chemical compounds has rapidly spread. Their results confirm the relationship between the inhibition of the functioning of the bone marrow under the influence of Diclofenac Sodium and the increased risk of the formation of altered cells, which then enter the bloodstream. In the future there are neurohumoral disorders, suppression of the body's natural protective forces, reactivity of the immune system. Many scientists have convincingly shown increased biological activity of NSAIDs against the background of immunodeficiency [6,7,8,9]. But the effect of the drug on a few germs of bone marrow cells remains at the same time.

The aim of the study is to analyze the various mechanisms of differentiation of red bone marrow stem cells, peripheral blood, erythrocytes, myelocytes under prolonged subtoxic action of Diclofenac Sodium on the body of white rats and pathogenetic justification of the principles of their early diagnosis and correction.

Due to the absorption of Diclofenac Sodium by the gastrointestinal mucosa (GIT), and binding to albumin in serum is responsible for an increase in its toxicity [5,9]. However, high risk of Diclofenac Sodium in damage to the gastrointestinal tract, impaired platelet aggregation, renal function. As a result of the action on the blood system, thrombocytopenia, hemolytic and aplastic anemia, as well as granulocytopenia develops. [6,7,8]. The effect of the drug on the bone marrow, where the formation of all blood cells occurs, remains unclear.

Analysis of literature showed that in the study of peripheral blood of rats, Diclofenac Sodium contributes to suppressing the amount of hemoglobin, red blood cells. The number of lymphocytes and granulocytes decreased. With long-term use, established drug toxicity, characterized by significant destruction of red blood cells, and leads to the development of anemia. The number of white blood cells, platelets and reticulocytes decreases significantly. Lymphopenia and granulocytopenia develop at the expense of a decrease in the incidence of nutrients in cells [11].

Morphologically, as a result of the toxic effect of Diclofenac in the Wistar line, the development of the chronic inflammatory process, which is manifested by reactive leukocytosis with a change in neutrophil cysts on the right, monocytopenia against the backdrop of compensatory manifestation of lymphocytosis, a significant increase in the level of ESR and the magnitude of thymol samples [4].

It was established from literary sources, that taking Diclofenac Sodium leads to bone marrow changes after 10 days of use, decreasing its mass. With prolonged use of the drug (for more than 20 days), there is a significant reduction in the mass of the bone marrow in the tubular bones. In addition, there are changes in the bone matrix, which has an unorganized lamellar structure.

In the analysis of cells of the myelocytic and erythrocytic series, a deviation of the normal ratio of myelocytes to erythrocytes is established. Up to 10 days of admission, the number of myelocyte germ increases, although changes are not significant. After a specified period of dosing in the bone marrow of rats, changes increase by 82.6% compared with control groups [12].

According to various sources, it was found that starting from 20 days the ratio of myelocytes to erythrocytes is 15.70% and gradually decreases to a small after 30 days of admission. The foregoing indicates the toxicity of the drug to the bone marrow in the first 10 days of treatment, which is gradually reduced. One can associate this with the activity of the immune system and some of the other factors that are currently not established. This can be observed when chemotherapy, in particular, the drug Methotrexate, is used [14].

Morphologically, myelocytes have nucleus fragmentation and occasional necrosis after using Diclofenac Sodium. The number of mature erythrocytes significantly decreases in contrast to the comparison group [15]. The indicated toxic effect can be related to the formation of an iminoquinone as a result of oxidation of 5-hydrosidiclofenac [13]. This substance is toxic to bone marrow cells.

With prolonged use of Diclofenac, there is a shortage of COX-2, which becomes a direct cause of delay or slowdown in the rate of proliferation of hematopoietic cells [16]. There is also the opinion that prolonged use of the drug is the cause of inhibition of renal prostaglandins, due to which the amount of erythropoietin is reduced. It has been established that prostaglandins contribute to the elevation of erythropoietin, which contributes to the appearance of new erythrocytes [12, 17].

Conclusions

1. Analysis of literary sources showed that when the drug Diclofenac Sodium is prolonged, the amount of red blood cells and peripheral blood cells in the experimental rats decreases. This, in turn, leads to the development of hemolytic and aplastic anemia;

2. According to various authors, the drug promotes the development of reactive leukocytosis in the peripheral blood with the shift of the neutrophil nucleus to the right, monocytopenia against the background of compensatory manifestation of lymphocytosis, a significant increase in the level of ESR and the value of the thymol sample;

3. Long-term administration of the drug clearly involves toxicity. This leads to significant destruction of erythrocytes, reduction of white blood cells, platelets and reticulocytes. Granulocytopenia is developing due to the reduced penetration of nutrients into the cell.

4. It has been determined from various sources that the use of the drug for more than 10 days contributes to the reduction of the erythrocytic bone marrow germ, and the increase in myelocytic count. The weight of the bone marrow also decreases. After 10 days of administration, toxicity is gradually reduced;

5. Morphologically, myelocytes have a fragmented nucleus and occasional necrosis. The number of mature erythrocytes is significantly reduced due to insufficient amount of erythropoietin;

6. Based on the foregoing, one can conclude that it is rational to use Diclofenac Sodium for up to 10 days.

Long-term administration can negatively affect the morphological and functional state of the bone marrow.

References

1. Danilova I. G. Vliyaniye sistemy fagotsitiruyushchikh mononuklearov na eritropoez v eritroblasticheskikh ostrovkakh kostnogo mozga / I. G. Danilova, B. G. Yushkov, M. V. Ulitko [i dr.] // Med. immunologiya. – 2006. - T. 8, N 2/3. - S. 135.
2. Leontyuk A. S. Osnovy vozrastnoy gistologii / A. S. Leontyuk, B. A. Sluka // Minsk :Vysheyshaya shkola, -2000, 418 s.
3. Deryvedmid' L.V. Kombinovani khondroprotektory pry likuvanni osteoartrytu / L.V. Deryvedmid', V.P. Vereitynova // Bil', suhloby, khrebet. – 2018. – Tom 8, №1. – S.31-36.
4. Hryshchenko V.A. Hematolohichnyy profil' u shchuriv pry eksperymental'nomu dyklofenak-indukovanomu hepatyti / A.V. Hryshchenko // UkrainianJournalofEcology. – 2017. – 7(3). – S.78–83.
5. Selyuk M.N. Novyye grani klassicheskogo nesteroidnogo protivovospalitel'nogo sredstva diklofenak / M.N. Selyuk, N.N. Kozachok, O.V. Selyuk // Suchasní preparati ta tekhnologíï. – 2013. – ML№8 (104). – S. 35-40.
6. Karateyev A.Ye. Ratsional'noye primeneniye nesteroidnykh protivovospalitel'nykh preparatov (NPVP) v klinicheskoy praktike / A.Ye. Karateyev, Ye.L. Nasonov, N.N. Yakhno i dr. // Sovremennaya revmatologiya. – 2015. – №1.15. – S. 7-23.
7. Karateyev A.Ye. NPVP-Gastropatiya: Dinamika za 12 let / A.Ye. Karateyev // Nauchno-prakticheskaya revmatologiya. – 2011. – №3. – S. 20-24.
8. Karateyev A.Ye. Ratsional'noye ispol'zovaniye nesteroidnykh protivovospalitel'nykh preparatov. Klinicheskiye rekomendatsii / A.Ye. Karateyev, Ye.L. Nasonov, V.T. Ivashkin i dr // Nauchno-prakticheskaya revmatologiya. – 2018. – №56(pril 1.). – S. 1-29.
9. Kozachok N.N. Nesteroidnyye protivovospalitel'nyye preparaty – kto lidiruyet v sovremennoy klinike? / N.N. Kozachok, M.M. Selyuk, S.A. Bychkova, N.G. Bychkova // Novosti meditsiny i farmatsii. – 2008. – №4(235).
10. Gladkikh F. V. Kharakteristika terapevtichnogo yefektu íbuprofenu ta yogo kombínatsíï z vínboronom za danimi gematologìchnikh pokaznikív na modelí ad'yuvantnogo artritu u shchurív / F. V. Gladkikh, N. G. Stepanyuk // ActamedicaLeopoliensia. – 2015. – T. 21, № 4. – S. 64-70.
11. OrinyaAgbajiOrinyaHaematologicalandbiochemicalstudies ontheeffectofdiclofenacSodiumonWistar Rattusnorvegicus / OrinyaAgbajiOrinya, AdeshinaYahayaAdenkola, RaphaelJohnOgbe // InternationalJournalofBiologicaland-ChemicalSciences. – 2016. – 10(5). – P. 2231-2242.
12. Chouhan S. Potential risks of aberration in bone histology and myelotoxity after continuous Diclofenac use in BALB/C mice model / S. Chouhan, S. Sharma // Proceedings of International Conference on Anthropogenic Impact on Environment & Conservation Strategy. – November 02 - 04, 2012, Ranchi.
13. Miyamoto, G., Zahid, N. and Uetrecht, J. P. 1997. Oxidation of diclofenac to reactive intermediates by neutrophils, myeloperoxidase, and hypochlorous acid. Chem. Res. Toxicol. 10(4): 414–419.
14. Sosin, M. and Handa S. 2003. Low dose methotrexate and bone marrow suppression. BMJ. 326: 266-267.
15. Merchant, M. A. and Modi, D. N. 2004. Acute and chronic effects of aspirin on hematological parameters and hepatic ferritin expression in mice. Indian J. Pharmacol. 36(4): 226-230.
16. Lorenz, M., Slaughter, H. S., Wescott, D. M., Carter, S. I., Schnyder, B., Dinchuk, J. E. and Car, B. D. 1999. Cyclooxygenase-2 is essential for normal recovery from 5-fluorouracil–induced myelotoxicity in mice. Exp. Hematol. 27: 1494–1502.
17. Fisher, J. W., Radtke, H. W., Jubiz, W., Nelson, P. K., Burdowski, A. 1980. Prostaglandins activation of erythropoietin production and erythroid progenitor cells. Exp. Hematol. 8: 65-89.

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