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Ліки – людині. Сучасні проблеми фармакотерапії і призна-
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Збірник містить статті і тези доповідей IV Міжнародної науково-практичної конференції «Ліки – людині. Сучасні проблеми фармакотерапії і призначення лікарських засобів», де розглядаються проблеми фармакотерапії захворювань людини, наводяться результати експериментальних та клінічних досліджень, аспекти вивчення й упровадження нових лікарських засобів, доклінічні фармакологічні дослідження біологічно активних речовин природного і синтетичного походження. Наведено також праці, присвячені особливостям викладання медико-біологічних і клінічних дисциплін у закладах вищої освіти.

Видання розраховано на широке коло наукових і практичних працівників медицини і фармації.

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CORRECTION OF CYTOKINE MISBALANCE BETWEEN PRO-INFLAMMATORY IL-1β AND ANTI-INFLAMMATORY IL-4 IN PATIENTS WITH CHRONIC GENERALIZED PERIODONTITIS

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Key words: cytokines, generalized periodontitis, pathogenesis, liposomes, quercetinum, lipoflavon

Introduction. Efficiency of local application of medical drugs in periodontal tissues depends on the display of substances in the periodontal pocket (PP), choice of medical substances, method of his application, contact with the gingival oral mucosa and maintainance of this concentration. Therefore it is necessary advantage to give to the forms and pathways of medications with the controlled and long action [5, 6]. Development and application high-efficiency and safe facilities of drug therapy of chronic generalized periodontitis (CGP) the last years legally considered one of priority directions of native and foreign researchers [1, 2, 3]. Medical local therapy is inalienable part of complex treatment of CGP [4].

Liposomes, owing to their small size, penetrate regions that may be inaccessible to other delivery systems. It is noteworthy that only liposomes have been largely exploited for drug delivery because the methods of preparation are generally simple and easy to scale-up. The aim of using liposomal carriers is generally, to increase the specificity towards cells or tissues, to improve the bioavailability of drugs by increasing their diffusion through biological membranes, to protect them against enzyme inactivation. These systems reduce the frequency of administration, further provide a uniform distribution of the active agent over an extended period of time [7, 11].

Cytokines play a major role in inflammatory and immune responses in periodontal tissues the patients with CGP. The misbalance between pro-inflammatory IL-1β and anti-inflammatory IL-4 mediators as being the cytokines for which there is the most substantial evidence for having a central role in cytokine networks in periodontal diseases [9, 10].

Anti-inflammatory properties of «Lipoflavon» (JSC „Biolek", Kharkov), which contained lecithin liposomes and quercetin are conditioned by his expressed anti-leukotrienes activity. Quercetin inhibits production of inflammation-producing enzyme 5-lipoxygenase (LOX). The immunomodulating action of Quercetinum is known. Quercetinum differentiated regulates expression genes of Th-1 (IFNγ) and Th-2 (IL-4) of cytokines by the normal mononuclear cells of peripheral blood. Quercetinum increased of phenotypical expression of IFNγ mononuclear cells of peripheral blood and suppressed IL-4 are positive mononuclear cells of peripheral blood, that is compared with the results of determination of mRNC/protein [8].

Therefore the comparative study of changes of pro-inflammatory IL-1β and anti-inflammatory IL-4 cytokines presents considerable theoretical and practical interest for local treatment the patients with CGP of initial-I degrees of severity with gel from the granules of Quercetinum (GQ) and liposomal Quercetinum-lecithin complex (LQLC).

The purpose of study was to increase of efficiency of complex treatment the patients with CGP of initial-I degrees of severity with gel from the granules of GQ and liposomal LQLC due to the correction of cytokine levels.

Material and Methods. The 35 patients with CGP of initial-I degrees of severity were observed. In accordance to treatment all patients were divided into 2 groups: I group – basic treatment with local application LQLC (18 patients) with the use of individual periodontal delivery tray; II group (group of comparison) – basic treatment with local application of gel from GQ (17 patients) with the use of individual periodontal delivery tray. The control group (C) included 14 healthy subjects without systemic inflammatory disease.

The patients of basic group was conduct base therapy with the local application LQLC (injection form of «Lipoflavon») as a suspension, prepared ex tempore, containing 137,5 mgs of lecithin and 3,75 mgs of Quercetinum. This suspension prepared at a premix 1/4 parts of content of small bottle with 5 ml 0,9% solution of natrium chloride, warmed-up to 38^0. The patients of comparison group was conduct base therapy with local application of gel from GQ with the use of individual periodontal delivery tray during 40 minutes 2 times per a day to 10 days.

All observed patients in the morning were conducted of mouth liquid (ML) before treatment and through 1, 6 and 12 months after treatment for immunological researches. Through 6 months of patients examined, inspected the condition of periodontal tissues and conducted supporting therapy, which included the professional hygiene of mouth cavity and local treatment using of individual periodontal delivery tray with gel from GQ and LQLC during 10 days for 40 minutes 2 times per a day, and also reception inward during 1 month of 1 g «Granules of Quercetinum» 2 times per a day.

Results and discussion. The patients of control group was mean IL-1β - 64,44 ± 6,2 pg/ml and anti-inflammatory IL-4 - 243,5 ± 17,48 pg/ml. The first mediators to have their role related to CGP pathogenesis were innate immunity cytokines produced after microbial recognition, such as IL-1β. These cytokines are produced by both resident cells (i.e. epithelial cells and fibroblasts) and phagocytes (i.e. neutrophils and macrophages) in periodontal environment. While the exact contribution of each cell type remains to be elucidated, previous studies described that a hyper-reactive phenotype of phagocytes is related to increased pro-inflammatory cytokines production in CGP [12].

Recent evidence also points to important roles of resident cells in periodontal bone loss, since the periodontal ligament fibroblasts and osteoclast precursors contact synergistically increases the expression of genes related to osteoclastogenesis, such as IL-1β [13]. IL-1β is produced by a wide range of periodontal tissues and immune cells and, as such, is considered to have multiple roles in innate and adaptive immune responses to plaque bacteria which feature in the pathogenesis of periodontitis. IL-1β acts (often in synergy with TNF-α and prostaglandin E2 (PGE2)) to induce many of the vascular changes associated with inflammation and in particular to regulate neutrophil emigration from the circulation into the periodontium. In adaptive immunity, IL-1β stimulates antigen presentation by APCs and influences T-cell development and phenotype. Studies of the expression of IL-1β, TNF-α, and PGE2 in oral fluids

and periodontal tissues in periodontal disease endorse the important role of these mediators in pathogenesis and, critically, this is supported by the results of investigations of their effect in animal models (including key studies using cytokine antagonists). Thus, IL-1β, TNF-α, and PGE2 will all activate osteoclast activity, MMP secretion, and alveolar bone resorption in chronic periodontitis [14, 15].

During the past decade numerous investigators have shown altered cytokine production in periodontitis and attemped to elucidate their role in periodontal diseases. For example, several studies have demonstrated that localized absence of IL-4 in diseased periodontal tissues is associated with periodontal disease activity and progression. Th2 cells commitment and action is primarily dependent of IL-4, the prototypical Th2 cytokine, which also acts as a B cell stimulatory factor. In addition to IL-4 is further believed to contribute to B cell differentiation and antibody production. Some studies propose that the Th2-type cytokine IL-4 may attenuate periodontitis progression, in contrast to its putative destructive role previously discussed. IL-4 has been asssociated to control other inflammatory diseases, such as periodontitis. In addition, there is a relative absence of IL-4-producing T cells at sites of inflammation. This imbalance is progressive, with decreasing levels of IL-4 correlated with loss of collagen and with increasing clinical severity. In addition, polymorphisms in the IL-4 promoter and intron that are associated with decreased serum levels of IL-4 are also associated with increased susceptibility to early onset periodontitis. It has been suggested that correcting this cytokine imbalance in chronic inflammatory conditions might be therapeutic [16, 17].

The patients with initial-I degrees of severity in the basic group before treatment was mean IL-1β - 123,2 ± 4,94 pg/ml, that was upper than 91 % in the C groups; IL-8 - 86,17 ± 1,84 pg/ml, that was upper than 40 % in the C groups; TNF-α - 44,91 ± 3,63 pg/ml, that was upper than 107 % in the C groups and anti-inflammatory IL-4 - 220,9 ± 11,89 pg/ml, that was lower than 9 % in the C groups. The patients in the comparison group before treatment was mean IL-1β - 122,6 ± 5,2 pg/ml, that was upper than 92 % in the C groups; IL-8 - 86,92 ± 3,54 pg/ml, that was upper than 41 % in the C groups; TNF-α - 45,29 ± 2,95 pg/ml, that was upper than 109 % in the C groups and anti-inflammatory IL-4 - 219,1 ± 7,74 pg/ml, that was lower than 10 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 1 month was mean IL-1β - 63,44 ± 3,03 pg/ml and anti-inflammatory IL-4 - 316,2 ± 10,73 pg/ml, that was lower than 30 % in the C groups. The patients in the comparison group after treatment through 1 month was mean IL-1β - 76,65 ± 5,21 pg/ml and anti-inflammatory IL-4 - 359,9 ± 10,36 pg/ml, that was lower than 48 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 6 month was mean IL-1β - 73,09 ± 6,97 pg/ml, that was upper than 15 % in the C groups and anti-inflammatory IL-4 - 292,2 ± 20,77 pg/ml, that was lower than 19 % in the C groups. The patients in the comparison group after treatment through 6 month was mean IL-1β - 85,22 ± 4,75 pg/ml, that was upper than 11 % in the C groups and anti-inflammatory IL-4 - 261,7 ± 16,25 pg/ml, that was lower than 17 % in the C groups.

The patients with initial-I degrees of severity in the basic group after treatment through 12 month was mean IL-1β - 68,57 ± 5,07 pg/ml, that was lower than 1 % in the C groups and anti-inflammatory IL-4 - 289,9 ± 10,91 pg/ml, that was upper than 1 % in the C groups. The patients in the comparison group after treatment through 12 month was mean IL-1β - 84,04 ± 4,17 pg/ml, that was lower than 6 % in the C groups and anti-inflammatory IL-4 - 244,8 ± 16,53 pg/ml, that was lower than 6 % in the C groups.

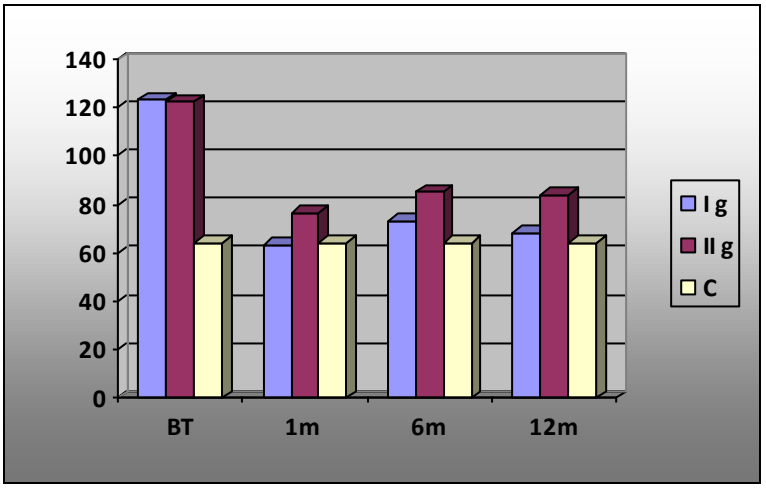

Fig. 1. Changes of cytokine level pro-inflammatory IL-1*β* in the ML before treatment and through 1, 6 and 12 months after treatment the patients with HGP of initial-I degrees of severity: I group (basic group) – basic treatment with local application LQLC; II group (comparison group) – basic treatment with local application of gel from GQ; C- control group.

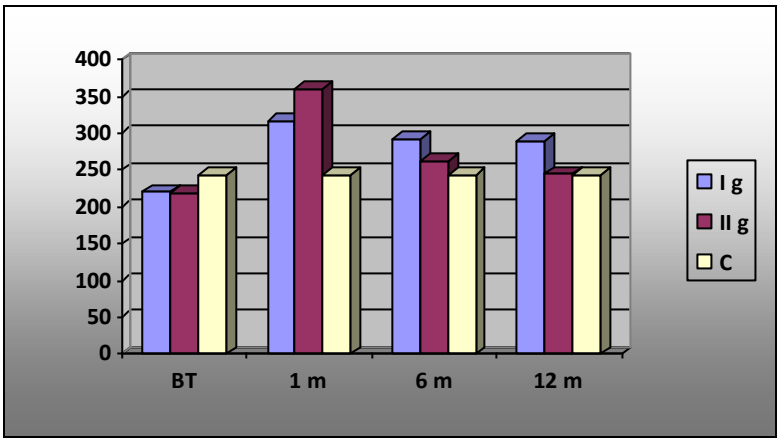

Fig. 2. Changes of cytokine level anti-inflammatory IL-4 in the ML before treatment and through 1, 6 and 12 months after treatment the patients with HGP of initial-I degrees of severity: I group (basic group) – basic treatment with local application LQLC; II group (comparison group) – basic treatment with local application of gel from GQ; C- control group.

Conclusions

The research in question demonstrates lipoflavon capability to normalize homeostasis of the oral cavity, normalize misbalance of cytokines in periodontal tissues, thus retarding process of inflammation and destruction of tissues and improving reparation of periodontal structures. High therapeutic efficiency of the liposomal quercetin-lecithin complex for patients with chronic generalized periodontitis, especially that of

initial-I degrees of severity was shown to be determined by anti-inflammatory, immunomodulating and periodontoprotecting effects. This allows to recommend lipoflavon for local application as pathogenetically substantiated drug in treatment of generalized periodontitis.

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MODULATION OF CATECHOLAMINE AND OTHER NEUTOMEDIATORS LEVELS IN ASCS

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Introduction. Currently there are a lot of reports in the literature about change of some protein levels including so called “neurospecific” regulatory peptides, a number of mediators, hormones, their metabolites and precursors in blood and other biological fluids under the effect of alcohol, narcotics, neuropsychic diseases, in hypnosis and its pharmacologic modeling’s [1, 4]. Activity of a number of enzymes, participating in the catecholamine metabolism, protein glycolyzation and other processes also undergo significant changes.

Thus, it was found, that process of schizophrenia included complex of specific pathochemical features which included a number of metabolic and hormonal signs opening the possibility to distinguish by metabolic hormonal status a patient with schizophrenia from a healthy person or a person suffering from other clinical variants of altered states of consciousness. In connection with above-mentioned, at present time the possibility of biochemical classification of depressive disturbances with case of discriminant multifactory analysis based on the evaluation of dynamics of indicators of urinary catecholamine and their metabolites is discussing the formula and the value of discriminant function for assessment of depression type has been offered [6, 7].

Improvement of the methods of molecularly biology, genetic cellulary engineering, on one side, and identification of some general tendencies in the biochemical changes in different pathologies or modifications of psychic states, on the other hand, manifested on the currently used conceptional approaches to biochemical diagnostic and therapeutic monitoring of these pathologies.

On the basis of rich literature data in this field we, in this work, tried to study some aspects of structural metabolic conception of cascade of biochemical changes manifesting in the case of different forms of altered states of consciousness (ASCs) [19].

These aspects are as follows:

- different neuropathologies, effect of hypnosis, narcotic analgetics or effect of stress-factors is considered as particular cases of altered states of consciousness;
- under the conditions of altered states of consciousness there are found structural metabolic rebuilding on the levels of different sites of CNS and peripheral nervous system, change of synthesis, secretion and catabolism of a number of hormones and mediators and first of all catecholamines and serotonin with consequent

changes in the membrane permeability, and system of intracellular signaling (cAMP, Ca++ ,others) and ion channels.

- structural metabolic rebuilding in altered status of consciousness are found in the tissues, blood and other biological fluids as in the form of rather universal manifestation (increase in molecule oxidative modification, disturbance of immunity and energy metabolism so on) so as in the specific set of changes in the activity of some enzymes, catecholamine level and NSB and ion homeostasis.
- uniformity of functional biochemical changes is postulated in alcoholism, narkomania and other states characteristic of ASCs during modeling of these interrelationships with hypnosis;
- improvement of the methodical approaches and adaptation of highly sensitive instrumental arsenal for biochemical and diagnostic monitoring of ASCs will allow further increase in informativity of the analysis of urine components, saliva, sweat, hair, expiratory air in order to obtain "molecular picture" of specific form of ASC.

What is the correlation between above-mentioned aspects of structural metabolic conception of the cascade of biochemical changes in ASC and literature data? It should be interesting to study in this connection some the most important data.

Conception of the Altered states of consciousness and regulatory peptides

As it was noted above, currently, the conception of altered state of consciousness has acquired the further development. With the use of special questionnaire the researchers of the Psychological Institute of Consultations and Investigations the standardized psychometric assessment of ASCs in humans has been carried out [24].

Investigations were performed as in the series of 11 experiments on 393 healthy subjects with use of different methods of induction of ASCs so as by screening of 1133 subjects in six countries. It was shown that psychometric analysis relating to this conception may be used for assessment of altered states of consciousness independently on the way of its induction.

The general denominator includes three types of altered states of consciousness, that is, syndrome of "oceanic boundlessness (OSE), "Dread of Ego Dissolution" (AIA) and Visionary Restructuralization (VUS).

Regulatory peptides (RP) are the class of endogenic compounds having an important role in the mechanisms of directed behavior with different biological modality, emotional states in ASCs (thirst, hunger, pain, aggression, fear and so on), as well as in the molecularly processes of homeostasis [16].

The effects of RP are mediated through classic cascades of the signaling systems and their components: cAMP, G-protein, nitric oxide and others It was shown that conjugated forms of RP are the class of information compounds having a significant role in the systemic organization of behavior forming on the basis of preliminary education. Many of endogenic RP have not only a free form, but also have forms of conjugated compounds, that is, complex compounds with blood proteins, biological fluids and intracellular proteins.

Conjugated forms of RP are characterized by marked ability of their molecules to change their conformations (as compared with native peptides) that, evidently, provides integration of hierarchically organized molecularly processes at all the stages of

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