UDC: 616.517-085.275.014.425 DOI: 10.14739/2310-1210.2016.5.82598

V. A. Visir, G. I. Makurina

Clinical efficiency and dermoprotection of 2-ethyl-6-methyl-3-hydroxypyridine succinate drug in case of psoriasis: from the antioxidation point of view

Zaporizhzhia State Medical University, Ukraine

Key words: *Antioxidants, PASI Index, Life Quality, 2-ethyl-6-methyl-3-hydroxypyridine Succinate, Clinical Study.*

Objective. To study the clinical significance of oxidative processes modulation within frames of 2-ethyl-6-methyl-3-hydroxypyridine succinate dermatropic efficiency assessment in patients with psoriasis affected by arterial hypertension.

Materials and methods. The results of this study are based on data of comprehensive examination and supervision of 30 patients suffering from psoriasis with different clinical forms such as normal levels of blood pressure (the control group) or in combination with hypertension (the study group).

Results. The comparative description of the antioxidative therapy efficiency was performed by the end of treatment. The findings showed significantly positive antioxidant-dependent mechanisms of 2-ethyl-6-methyl-3-hydroxypyridine succinate clinical efficiency in patients with psoriasis affected by arterial hypertension.

In case of patients with combined psoriasis and essential hypertension course 2-ethyl-6-methyl-3-hydroxypyridine succinate therapy caused reliable decrease of free-radical oxidation intensification in particular nitrosative (reliable decrease of nitrotyrosine) and oxidative (negative dynamics of endothelin-1 and positive dynamics as to glutathione metabolism) stresses. That, in its turn, decreased the evidence of apoptotic and inflammatory processes (caspase-8 and TNF-α regress) both directly and indirectly by means of mediating anti-inflammatory effect on endothelium cells and macrophages of anticoagulant proteinase through endothelial protein C receptor (EPCR) with production of components and structures of extracellular matrix and disturbance of microcirculation. Thus, it determines the key pathogenetic aspects of psoriasis. The decrease of VEGF expression indicators level (vascular endothelial growth factor) and serotonin, associated with this combined therapy, had stipulated statistically significant positive clinical and subjective effect in form of regress of dermatological changes (PASI index), decrease of itch (optimization of serotonin biosynthesis and reduction of methionine conversion (with homocysteine formation)) and improvement of life quality.

Conclusions. Taking into account potential influence of 2-ethyl-6-methyl-3-hydroxypyridine succinate on these pathophysiological predictors and pathogenesis, which are to some extent involved in formation and progression of psoriatic disease, use of 2-ethyl-6-methyl-3-hydroxypyridine succinate is sufficiently effective in conditions of psoriasis therapy optimization.

Zaporozhye medical journal 2016; №5 (98): 31–38

Клінічна ефективність і дермопротекція 2-етил-6-метил-3-гідроксипіридину сукцинату при псоріазі: погляд із позицій антиоксидації

В. А. Візір, Г. І. Макуріна

Рекомендації щодо терапії пацієнтів, які страждають одночасно на псоріаз та артеріальну гіпертензію, вкрай нечисленні.

Мета роботи – вивчити клінічну значущість модуляції оксидативних процесів у рамках оцінювання дерматотропної ефективності 2-етил-6-метил-3-гідроксипіридину сукцинату у хворих на псоріаз на тлі артеріальної гіпертензії.

Матеріали та методи. Результати цього дослідження засновані на даних комплексного обстеження та спостереження за 30 пацієнтами, які страждають на різні клінічні форми псоріазу як з нормальними цифрами артеріального тиску (контрольна група), так і в поєднанні з артеріальною гіпертензією у вигляді гіпертонічної хвороби (основна група).

Результати. Здійснили порівняльну характеристику антиоксидантної ефективності терапії наприкінці лікування. Дані показали доволі позитивні антиоксидант-залежні механізми клінічної ефективності 2-етил-6-метил-3-гідроксипіридину сукцинату у хворих на псоріаз на тлі артеріальної гіпертензії.

У хворих із поєднаним перебігом псоріазу та гіпертонічної хвороби терапія 2-етил-6-метил-3-гідроксипіридину сукцинатом сприяла вірогідному зниженню проявів інтенсифікації вільно-радикального окислення, зокрема нітрозуючого (вірогідне зменшення нітротирозину) та оксидативного (негативна динаміка ендотеліну-1 і позитивна щодо метаболізму глутатіону) стресів, що, своєю чергою, зменшувало вираженість апоптотичних і запальних процесів (регрес каспаз-8 і ФНП-альфа) як безпосередньо, так і опосередковано через дію антикоагулянтної протеїнази на клітини ендотелію та макрофаги через ендотеліальний рецептор протеїну С (EPCR), регулюючи продукцію компонентів і структур екстрацелюлярного матриксу з порушенням мікроциркуляції, детермінуючи таким чином ключові патогенетичні аспекти розвитку псоріазу. Зниження рівня показників експресії VEGF (регулятор утворення мікросудин) і серотоніну на тлі цієї комбінованої терапії зумовлювало статистично значущий позитивний клінічний і суб'єктивний ефект у вигляді регресу дерматологічних змін (індекс PASI), зменшення свербежу (оптимізація біосинтезу серотоніну та редукція конвертації метіоніну з утворенням гомоцистеїну), поліпшення якості життя.

Висновки. З урахуванням потенційного впливу 2-етил-6-метил-3-гідроксипіридину сукцинату на відзначені патофізіологічні предиктори та ланки патогенезу, які в однаковій мірі залучаються при формуванні та прогресуванні псоріазу, можна зробити висновок: застосування цього препарату є доволі перспективним у плані оптимізації терапії досліджуваного дерматозу.

Ключові слова: *антиоксиданти, індекс PASI, якість життя, 2-етил-6-метил-3-гідроксипіридину сукцинат, клінічне дослідження.*

Запорізький медичний журнал. – 2016. – №5 (98). – С. 31–38

Клиническая эффективность и дермопротекция 2-этил-6-метил-3-гидроксипиридина сукцината при псориазе: взгляд с позиций антиоксидации

В .А. Визир, Г. И. Макурина

Рекомендации относительно терапии пациентов, страдающих одновременно псориазом и артериальной гипертензией, крайне малочисленны.

Цель работы – изучить клиническую значимость модуляции оксидативных процессов в рамках оценки дерматотропной эффективности 2-этил-6-метил-3-гидроксипиридина сукцината у больных с псориазом на фоне артериальной гипертензии.

Материалы и методы. Результаты этого исследования основаны на данных комплексного обследования и наблюдения за 30 пациентами, страдающими различными клиническими формами псориаза как с нормальными цифрами артериального давления (контрольная группа), так и в сочетании с артериальной гипертензией в виде гипертонической болезни (основная группа).

Мы провели сравнительную характеристику антиоксидантной эффективности терапии к окончанию лечения. Полученные данные показали достаточно позитивные антиоксидант-зависимые механизмы клинической эффективности 2-этил-6-метил-3-гидроксипиридина сукцината у больных с псориазом на фоне артериальной гипертензии.

Результаты. У больных с сочетанным течением псориаза и гипертонической болезни терапия 2-этил-6-метил-3-гидроксипиридина сукцинатом способствовала достоверному снижению проявлений интенсификации свободно-радикального окисления, в частности нитрозирующего (достоверное уменьшение нитротирозина) и оксидативного (негативная динамика эндотелина-1 и позитивная в отношении метаболизма глутатиона) стрессов, что в свою очередь уменьшало выраженность апоптотических и воспалительных процессов (регресс каспазы-8 и ФНО-альфа) как напрямую, так и косвенно, опосредуя противовоспалительное действие антикоагулянтной протеиназы на клетки эндотелия и макрофаги через эндотелиальный рецептор протеина С (EPCR), регулируя продукцию компонентов и структур экстрацеллюлярного матрикса с нарушением микроциркуляции, детерминируя таким образом ключевые патогенетические аспекты развития псориаза. Снижение уровня показателей экспрессии VEGF (регулятор образования микрососудов) и серотонина на фоне этой комбинированной терапии обусловливало статистически значимый позитивный клинический и субъективный эффект в виде регресса дерматологических изменений (индекс PASI), уменьшения зуда (оптимизация биосинтеза серотонина и редукция конвертирования метионина с образованием гомоцистеина), улучшения качества жизни.

Выводы. С учётом потенциального влияния 2-этил-6-метил-3-гидроксипиридина сукцината на указанные патофизиологические предикторы и звенья патогенеза, которые в той или иной степени вовлекаются при формировании и прогрессировании псориаза, можно сделать вывод, что применение этого препарата является достаточно перспективным в плане оптимизации терапии изучаемого дерматоза.

Ключевые слова: *антиоксиданты, индекс PASI, качество жизни, 2-этил-6-метил-3-гидроксипиридина сукцинат, клиническое исследование.*

Запорожский медицинский журнал. – 2016. – №5 (98). – С. 31–38

Relevance

Psoriasis, being one of the most widespread chronic diseases in the world, has its share of approx, 2–3 % of the world people in structure of general disease incidence and it makes 12–15 % in the structure of general dermatologic diseases incidence [1,2]. During last years there was formed the vector of serious and torpid psoriasis forms growth that is undoubtedly interesting for researchers and specialists. This dermatosis is considered as genetically determined disease which proceeds as inflammatory process in derma with disorder of proliferation and differentiation of keratinocytes under effect of different trigger factors [3,4]. In spite of many researches none of the existing hypotheses is recognized up to now. The most widespread hypotheses are genetic, neurogenic, viral, metabolic and immunologic [5–7].

Taking into account all updated etiology and pathogenesis concepts obtained due to scientific researches of the last years the psoriasis is considered as typical pathologic inflammatory process in conditions of antioxidant defense systems functional insufficiency and overexpression of apoptotic receptors and also disorder of thiol-disulfide balance. It permits us to make corrections in existing psoriasis treatment regimens, taking into account the above mentioned pathogenetic links [8]. Hyperstimulation of malpighian layer cells proliferation in case of inflammation and in conditions of high antioxidative activity lead to the abrupt increase of speed for movement of keratinocytes to the outside under apoptotic influence of atmospheric oxygen and its reactive species causing the apoptotic death of keratinocytes with evident expression of apoptotic receptors [9,10]. Oxidative stress of keratinocytes which didn't pass the differentiation stage – is the trigger mechanism for formation of defective corneous layer – the psoriatic process key link. Besides the antioxidative system activity is considerably changed in particular due to increase in ceruloplasmin concentration and decrease in α-tocopherol, that indicates the available inflammatory syndrome. Free radicals which are formed due to lipid peroxidation have very important pathogenetic role in inflammation of epidermis development in case of psoriasis [11,12].

In case of comorbide conditions, in particular, if the patient simultaneously has psoriasis and essential hypertension at the beginning of oxidative stress development the moderately increased oxidative activity of plasma and erythrocytes is compensated by rise of vitamin E effect in plasma and effect of superoxide dismutase (SOD) and glutathione peroxidase in erythrocytes. Progress of comorbide pathology is accompanied by intensification of free-radical oxidation and decrease of thiol-disulfide ratio which are not compensated by activation of the main antioxidative systems of plasma and erythrocytes [13,14]. Decompensated stage of the oxidative stress which is typical for more serious category of patients includes the evident intensification of all pro-oxidant reactions, total depression of antioxidative systems, high oxidation rate of low density lipoproteins, endogenous toxemia and disorder of the cell cytosolic and membranous structures. Oxidative and modified low density lipoproteins and proteins – the substances of low and medium molecular mass, metabolites of free-radical oxidation are the factors of endogenous intoxication [15].

Considering peculiarities of pathogenesis of psoriasis combined with essential hypertension, one of the key aspects in complex treatment regimen with comorbide pathology is the drugs with evident antioxidative and antihypoxant effects. Based on earlier performed researches of different pathogenetic links in order to increase efficiency of psoriasis therapy the nootropic drug "Semax" and hepatoprotector with evident antidepressant effect "Geptor" are started to be included into complex treatment regimen additionally to the standard therapy [16]. "Semax" has evident antioxidant, antihypoxant, psychostimulation and neurotrophic effect. The drug has direct effect on molecular

trigger mechanisms, normalizes cytokine balance, increases the level of anti-inflammatory factors, decreases formation of nitric oxide, causes suppression of lipid peroxidation processes, activates synthesis of superoxide dismutase and decreases the level of cyclic guanosine monophosphate. "Geptor" has detoxic, regenerative, antioxidative, antifibrosing and neuroprotective properties. It fills up deficiency of ademetionine and stimulates its generation in organism, first of all in the liver and brain [17].

Among existing drugs of antioxidative group in the modern medicine the attention is paid to the drugs with multi-modal complex effect as to the oxidative stress, for example: succinic acid derivative – ethylmethylhydroxypyridine succinate (2-ethyl-6-methyl-3-hydroxypyridine succinate). 2-ethyl-6-methyl-3-hydroxypyridine succinate as the most important component of Krebs cycle and reactions of adenosine triphosphate (ATPh) biosynthesis and as antioxidant is especially interesting due to its available double protective mechanism – blocking of free radicals formation and their "trap" owing to inhibition of lipid peroxidation at the earliest stages and, respectively, normalization of oxidative phosphorylation processes and ATPh synthesis. Besides, this drug activates the most important link of the organism antioxidative system-superoxide dismutase enzyme, normalizes content of lipid fractions, decreases cholesterol/phospholipids index in the cell membranes, decreases parameters of the membrane microdensity, i.e. it has wide range of effect as membrane stabilizer [18,19].

Today there is no doubt in importance and actuality of new chemical compounds search which have antioxidative properties and on the basis of which there can be created the medicinal drugs which are perspective for treatment of such diseases as psoriasis and essential hypertension as separate nosologic units and in combined mutually aggravating course. Taking into account the connection between chemical structure and targets of antioxidant effect is the required background for targeted search of new antioxidants with certain targets of effect and preliminary specified properties for more effective treatment of appropriate diseases, in development of which the key role belongs to some links of free-radical oxidation for obtaining the reliable results of dermoprotective effect.

Objective. To study clinical significance of oxidative processes modulation within frames of 2-ethyl-6-methyl-3-hydroxypyridine succinate dermatotropic effect assessment in patients with psoriasis associated with arterial hypertension.

Materials and methods

Results of the present study are based on data of complex examination and dynamic supervision of 30 patients with different clinical forms of psoriasis (PS) at the progressive stage (widespread vulgar, exudative and diffuse psoriasis) in combination with essential hypertension (EH) (age was from 25 to 70, 18 men and 12 women, duration of PS and EH was 4.1±0.7 and 7.2±0.9 years respectively). Patients were treated in department of Zaporizhzhia Regional Dermatovenerologic Clinical Dispensary of Zaporizhzhia Region Council; and they suffered from arterial hypertension (AH) in form of essential hypertension (EH).

Lesion of the skin was widespread in 65 % of patients. The majority of patients (more than 70 %) had repeated relapses within year. According to anamnesis the aggravating psoriasis heredity was identified in 4 patients. The winter type of psoriasis was identified in 16 patients, the summer type – in 2, undifferentiated type – in 12.

Psoriasis was detected according to Adapted Clinical Guide (2013) for psoriasis diagnostics and treatment. Essential hypertension was detected respectively in accordance with Recommendations of Cardiologist Association of Ukraine (2013). All patients gave written consent for participation in the research. According to information of complex clinical-anamnestic and instrument-laboratory examination all patients have no data as to the presence of chronic kidney diseases or lesion of kidney vessels. In order to estimate psoriasis severity there was used Psoriasis Area and Severity Index (PASI) which is objective clinical system for determination of the body surface affected area and intensity of the main dermatosis symptoms. In order to estimate life quality of patients the Dermatology Life Quality Index (DLQI) was determined through filling in the Dermatology Life Quality Index questionnaire.

All patients had standard treatment in conditions of dermatological department (desensitizing, anti-inflammatory, sedative drugs, hepatoprotectors, A, C vitamins groups and 2 % salicylic and sulphur-salicylic ointments for external application) with simultaneously traditional adequate antihypertensive individually selected therapy.

All patients were divided by random on 2 groups, 15 persons each, comparable under the main clinical and dermatological parameters. In the first group the traditional therapy was added by 2-ethyl-6-methyl-3-hydroxypyridine succinate (2-ethyl-6-methyl-3 hydroxypyridine succinate) in dose of 4 ml (200 mg) intravenously, by drop infusion 1 time per day within 10 days with further oral dosing of 500 mg (course duration is 1 month). Determination of TNF-α and Caspase-8 levels in the blood serum was performed by indirect enzyme-linked immunosorbent assay using sets of Bender MedSystems GmbH (Austria) according to instructions to the sets in vitro conditions. High sensitivity and accuracy of determination was stipulated by special binding of antigens with appropriate antibodies immobilized at the bottom of microwell that ensures capture of the target protein. The captured protein was detected by means of biotin-conjugated antibodies. Amplification of generated signal was performed by means of horseradish peroxidase enzyme (HRP) with further colorimetric determination at the wave length of 450 nm. Intensity of color developed after incubation with tetramethylbenzidine (TMB) substrate was proportional to quantity of antigen in the sample. For quantitative determination of TNF-α and Caspase-8 content in the blood serum samples the appropriate standard curves were used. Results of quantitative determination of TNF-α were shown in pg/ml and for Caspase-8 – in ng/ml.

Determination of endothelin-1, homocysteine, vascular-endothelial growth-stimulating factor A (VEGF-A), protein C endothelial receptor (EPR), serotonin in the blood serum was performed by method of indirect enzyme-linked immunosorbent assay using sets of Bender MedSystems GmbH (Austria) and determination of nitrotyrosine was pereformed by means of set of Hycultbiotech (Netherlands) according to instructions to the sets in vitro conditions. Research was performed based on immunological department of Training Medical and Laboratory Center of Zaporizhzhia State Medical University by means of

Digiscan SA 400 flatbed semi-automatic immunoenzymometric analyser of Asys Hitech (Austria, serial No.70384, the Head is Abramov A.V.).

The level of renewed and oxidated glutathione with further calculation of its ratio was estimated fluorometrically. The principle of the method is based on interaction of ortho-phthalic anhydride with renewed glutathione resulting in formation of fluorescent complex which is registered fluorometrically. In studied groups the activity of superoxide dismutase (SOD) was determined. The principle of the method is based on the fact that SOD competes with nitroblue tetrazolium (NBT) for superoxide radicals being formed due to aerobic interaction of NADH and phenazine methosulfate (PhMS). As the result of this reaction NBT is renewed to hydrazine tetrazole. If SOD is presented the percent of NBT renewal is changed.

Obtained studied values are presented in such form: sample average value ± standard error of the average value. Normality of distribution was estimated under criteria of Kolmogorov-Smirnov (D). The results are presented as the average value and standard error of representativeness of sample average value and as median and interquartile range (25–75 percentiles if difference from the normal disturbance is). Comparison of groups according to qualitative character and during study of indices incidence degrees was performed by means of χ^2 criterion with analysis of contingency Tables. Estimation of differences was performed by means of Wilcoxon criterion. The results of research were processed using statistical license software package "Statistica® for Windows 6.0" (StatSoft Inc., No. AXXR712D833214FAN5) at the department of Medical Information Science of ZSMU and also by means of SPSS 16.0, Microsoft Excel 2013. Separate statistical procedures and algorithms are implemented as specially written macros in the appropriate programs. The differences are considered reliable at the significance level of $p<0.05$.

Results and discussion

Analysis of dynamics in indicators of index PASI and assessment of the life quality under DLQI showed the reliable positive effect of 2-ethyl-6-methyl-3-hydroxypyridine succinate addition to the traditional treatment regimen of PS. Thus, assessment of severity of psoriatic lesion under PASI scale during course of treatment with 2-ethyl-6-methyl-3-hydroxypyridine succinate revealed the successive decrease in number of the studied index points of all patients. The average value of DLQI after treatment with 2-ethyl-6-methyl-3-hydroxypyridine succinate was more reduced than in case of traditional therapy; this fact indicates the more evident improvement of life quality in the 1st group of patients. There was noted that figures of PASI and DLQI shifts in the 1st group were higher than in the 2nd one; this fact indicates the more evident dynamics of psoriasis solution for patients who had taken 2-ethyl-6-methyl-3-hydroxypyridine succinate comparing to disease course of patients who had been treated according to the standard regimen. The indicator of reliable effectiveness of therapy – decrease of PASI by 75 % (PASI 75) was revealed in 66.7 % of patients, the rest 4 patients – decrease of PASI by 50 % in comparison with the therapy start and 1 patient – decrease below PASI 50 that is stipulated by psoriasis arthropica presence; in such case it is difficult to estimate the condition because it is subjective aspect (sense of pain and restraint). Rate of obtaining PASI 75 was statistically significantly higher than in the 1st group comparing to the 2nd one ($\chi^2=9.87$ if $p<0.05$).

In group of patients who had taken 2-ethyl-6-methyl-3-hydroxypyridine succinate together with complex therapy the leveling of the main symptoms (erythema, infiltration, desquamation etc.) was more intensive than in the control group ($\chi^2=11.7$ if $p<0.01$) and clinical signs of PS in the 1st group completely disappeared or significantly decreased, especially itch. Clinical dynamics in the second group was less evident and indicant, moreover in 7 cases the condition remained almost without dynamics.

The important result of the work was the change of the patient staying in hospital department duration: treatment duration associated with use of 2-ethyl-6-methyl-3-hydroxypyridine succinate made 18.4±0.63 in average and after the standard therapy it made 24.9±0.91 bed-days that indicates statistically significant ($p<0.05$) decrease in therapy terms in group of patients who had taken this drug.

We performed the comparative analysis of the therapy antioxidative effectiveness by the end of treatment. Obtained data showed sufficiently positive antioxidant –dependent mechanisms of 2-ethyl-6-methyl-3-hydroxypyridine succinate clinical effectiveness in patients with psoriasis associated with arterial hypertension.

Let's consider the obtained values of patients in the study groups influenced by therapy. The results of groups are shown in *Table 1*.

As can be seen from the data, there was a tendency to reduce the level of caspase-8 at 42.86 % ($p>0.05$) after applying standard regimen 2-ethyl-6-methyl-3-hydroxypyridine succinate, not exceeding in absolute values the level of caspase-8 to the end of treatment than the level of caspase-8 in patients without this drug prescription in the second group (7.69 %); that indicates the decrease of its role as proximal caspase in death of the epidermis cells by means of tumor necrosis factor (TNF) family receptors activation. Epidermal keratinocytes of the skin are programmed for spontaneous death which progresses from stratum to corneous layer of epidermis. These cells express all known caspases including caspase-8 and can be activated by ligands of TNF family by means of caspase depending way. Activation of this caspase-mediated process of the cell death enables pathological damage of epidermis. It is noted that reliable ($p<0.05$) synchronous 28.54 % TNF-α level decrease in the first group of patients using 2-ethyl-6-methyl-3-hydroxypyridine succinate, and in the second group this indicator decreased to 9.41 % that confirms the idea about more active course of inflammatory process in the skin if TNF-α value is greater and without use of antioxidants in treatment regimen. Ability of TNF-α to attack different cells in the skin leads to induction of other inflammatory cytokines, chemokines and such growth factors as 5, 6, 7 types molecules of endothelial adhesion.

After course of treatment of the first group patients with 2-ethyl-6-methyl-3-hydroxypyridine succinate there was noticed reliable decrease of such indicator level as VEGF (vessel endothelium growth factor) by 26.04 % ($p<0.05$) and in the second group the decrease of VEGF level made 8.11 %. Decrease of VEGF indicators leads to reduction of endothelium cells hyper-

Table 1

Studied indicators of the examined persons influenced by the therapy

Indicator, units of measurement	1 group		Value of differences	2 group		Value of differences
	Initially (n=15)	After therapy (n=15)		Initially (n=15)	After therapy (n=15)	
Caspase-8, ng/ml	0.14 (0.12–0.16)	0.11 (0.07–0.15)	-21.43 %	0.13 (0.11–0.18)	0.14 (0.12–0.16)	+7.69 %
Level of TNF-α, pg/ml	21.44 (16.2–22.8)	15.32 (12.61–18.41)*	-28.54 %	22.31 (18.3–25.21)	20.21 (17.5–23.73)	-9.41 %
VEGF, pg/ml	434.21 (344.4–523.6)	321.14 (264.6–382.5)*	-26.04 %	509.67 (411.3–623.8)	468.36 (264.66–582.4)	-8.11 %
Nitrotyrosine, nmole/ml	11.61±1.29	8.07±0.97*	-30.49 %	12.53±1.09	14.51±1.57	+15.80 %
Serotonin, ng/ml	190.13±18.26	121.09±10.6*	-36.31 %	178.1±23.2	167.0±14.96	-6.23 %
Endothelin-1, pmole/ml	0.88±0.09	0.53±0.06*	-39.77 %	0.81±0.08	0.73±0.09	-9.88 %
Homocysteine, mmole/ml	16.12±0.94	12.33±1.05*	-23.51 %	15.57±1.1	17.07±1.34	+9.63 %
Endothelial protein C receptor, ng/ml	950.71±38.14	713.45±41.6*	-24.96 %	914.69±45.1	908.2±52.68	-0.71 %

Note: * – $p<0.05$ in comparison with initial values.

proliferation, invasion of endothelial cells in vascular matrix, limits formation of new capillaries; that in general slows down the pathological angiogenesis process with combined course of psoriasis and EH. At that the more obvious decrease of VEGF indicator was noticed after application of 2-ethyl-6-methyl-3-hydroxypyridine succinate antioxidant.

With 2-ethyl-6-methyl-3-hydroxypyridine succinate treatment the patients of both groups also had decrease in serotonergic systems activity that became apparent in reliable ($p<0.05$) decrease in serotonin level in the first group by more than 1/3 (36.31 %) in the first group and in the second group by 6.23 % that indicates considerable increase in efficiency of psoriasis standard therapy combined with EH, if 2-ethyl-6-methyl-3-hydroxypyridine succinate is used in the treatment regimen, because serotonin is very important in cell apoptosis regulation in case of psoriasis. The level of such considerable indicator of nitrosative stress in organism as nitrotyrosine has decreased after performed treatment. In the first group the indicator is reliably ($p<0.05$) decreased by 30.49 % and in the second one – by 15.80 % that shows limitation of nitrosation processes and consequently decrease of epidermis cell death and damage of vascular endothelium that generally leads to stable disease remission.

Endothelin-1 is biologically active peptide of wide application range which is one of the most important regulators of endothelium functional condition and morphologically coupled with blood, on the one part, and coupled with muscular vessel wall, on the other part. Its vasoconstrictive effects are accompanied by changes of system and regional hemodynamics. During complex treatment there was noticed the decrease of endothelin-1 level reliably ($p<0.05$) by 39.77 % in group of patients with 2-ethyl-6-methyl-3-hydroxypyridine succinate therapy and without use of 2-ethyl-6-methyl-3-hydroxypyridine succinate the endothelin-1 decrease level made 9.88 % that yields to indicators of the first group patients in treatment effectiveness.

Endothelial protein C receptor (EPCR, CD201) is membrane protein, receptor having the important role in activation of protein C: EPCR intensifies activation of protein C at the effect of thrombin-thrombomodulin complex and participates in transfer of the signal mediated by protein C which controls the blood coagulation. Endothelial receptor of protein C is considerably expressed in endothelial cells of coronary arteries and skin capillaries. Treatment of patients with 2-ethyl-6-methyl-3-hydroxypyridine succinate has reliably decreased in the indicator of endothelial protein C receptor by 24.96 % ($p<0.01$) and therapy without 2-ethyl-6-methyl-3-hydroxypyridine succinate use – by 0.71 %. These results permit to make conclusion about absence of considerable influence of the standard psoriasis and EH therapy without use of antioxidants on EPCR indicator and severity of comorbide pathology course.

Therapy of psoriasis and EH with use of 2-ethyl-6-methyl-3-hydroxypyridine succinate has decreased values of homocysteine reliably ($p<0.05$) by 23.51 % in the blood of patients and without 2-ethyl-6-methyl-3-hydroxypyridine succinate use – by 9.63 % that also shows decrease of oxidative stress processes activity and limitation of pathological process in epidermis. Reliable positive connections between level of homocysteine and EH was confirmed by many researches, besides homocysteine is the predictive marker of fatal outcome due to cardiovascular diseases.

Changes of glutathione metabolism by the end of therapy course are shown in *Table 2*.

After use of 2-ethyl-6-methyl-3-hydroxypyridine succinate in the standard therapy there was determined the logically reliable increase of renewed thiols by 27.65 % ($p<0.05$) in the first group of patients and in the second group there was noticed only tendency to increase of renewed thiol level which made 4.52 % (reactions is not valid). Level of oxidated glutathione was reliably ($p<0.05$) decreased in the first control group by 33.01 % after treatment and in the second group – was decreased by 11.76 %. Increase of reserves of renewed thiols in organism indicates the considerable reserve of antioxidative system and positive influence of performed treatment. High redox-activity of glutathione and simultaneously considerable stability to oxygen oxidation, significant concentration in the cell and ability to save its renewed condition make it the very important redox-buffer of the cell internal environment. During protection of the cell

Table 2

Dynamics of glutathione metabolism of the examined patients on treatment

Indicator, units of measurement	1 group		% Value of differences	2 group		% Value of differences
	Initially (n=15)	After therapy (n=15)		Initially (n=15)	After therapy (n=15)	
Renewed glutathione, μmol/l	15.3±0.41	19.53±0.46*	+27.65 %	15.5±0.45	16.2±0.29	+4.52 %
Oxidated glutathione, μmol/l	3.12±0.05	2.09±0.07*	-33.01 %	3.4±0.04	3.8±0.05	+11.76 %
Ratio of renewed./oxid. form, c.u.	4.9±0.23	9.34±0.29*	+90.61 %	4.56±0.21	4.26±0.15	-6.58 %
SOD, c.u./mg protein/min	21.13±1.24	52.56±1.09*	+148.75%	20.41±1.51	21.63±1.94	+5.98 %

Note: * – $p<0.05$ in comparison with initial values.

structures from free radicals glutathione is the electrons supplier for peroxydases.

Increment of renewed/oxidated glutathione forms ratio in the first group of patients made 90.61 % reliably ($p<0.05$) after 2-ethyl-6-methyl-3-hydroxypyridine succinate therapy and the second group was marked by less significant dynamics in change of the studied indicator after standard therapy which made 6.58 %. This fact confirms our conclusions about increase of antioxidative system reserve after 2-ethyl-6-methyl-3-hydroxypyridine succinate use and limit of oxidative stress processes in organism. Also in the first experimental group SOD reserves in organism increased by 148.75 % reliably ($p<0.05$) after treatment with 2-ethyl-6-methyl-3-hydroxypyridine succinate and in the second group SOD activity increased by 5.98 % after treatment. SOD as polyfunctional compound catalyzes dismutation reaction of superoxide-anion radical with formation of hydrogen peroxide and oxide, ensuring protection of organism from biological oxidants and stability of the cell in oxidative stress conditions. Increase of SOD mentioned by us probably has adaptive character in oxidation conditions in case of PS. According to performed analysis of contingency matrices within frames of carrying out the correlation adaptometry for assessment of clinical therapy effectiveness there were obtained data stated that: in the first group after treatment with 2-ethyl-6-methyl-3-hydroxypyridine succinate the structure of tightness of correlation interactions was less evident and reliable than in the second group. It is informatively and objectively indicated by value of calculated weight of correlation column G (the 1st group is 8.7 before the treatment and 6.4 after the treatment; the 2nd group is 9.1 before the treatment and 8.5 after the treatment) that shows efficiency of performed therapy for both groups but more apparent and evident for the first group.

Discussion of the obtained results

It is important to mention that 2-ethyl-6-methyl-3-hydroxypyridine succinate is the drug with unique clinical and pharmacological range. It is based on original triple mechanism of direct influence drug action on oxidative metabolism processes of the organism cells. First of all, this influence refers the correction of basic biochemical processes in the skin cells, endothelium of vessels damages due to activity of ischemic and autoimmune factors and consists of direct antioxidative action (binding of free radicals – reactive oxygen species and hydroperoxides formed in hypoxia conditions) and protection of the cell membranes (the external and internal membranes – mitochondrial ones). It enables realization of protective effect relative to the main membrane-bound enzymes (adenylate cyclase, phosphodiesterase, etc.) Besides 2-ethyl-6-methyl-3-hydroxypyridine succinate has indirect antioxidative influence (activation of natural antioxidative system – catalase and superoxide dismutase enzymes, glutathione biosynthesis), activates the main link of Krebs cycle – succinate dehydrogenase enzyme and, respectively, succinate dependent reactions which directly determine accumulation of macroergic phosphates (adenosine triphosphates, adenosine diphosphate) that, in its turn, leads to decrease of lactate concentration and prevents development of lactate acid acidosis and serious shifts of acid-base balance. One of the important moments in multiple-factor mechanism of this drug action is its ability to improve the blood rheological properties and also evident hypo-lipid effect.

Prescription of 2-ethyl-6-methyl-3-hydroxypyridine succinate for the patients with such combined pathology as essential hypertension and psoriasis can stimulate decrease of objective and subjective symptoms and improvement of life quality due to favorable influence on pathogenetic mechanisms of oxidative stress. 2-ethyl-6-methyl-3-hydroxypyridine succinate also can inhibit the formation of free radicals with activation of synthesis of prostaglandins and leukotrienes – the main link of the cell damage at the further stages of pathophysiological reactions in case of psoriasis and essential hypertension. Effective use of 2-ethyl-6-methyl-3-hydroxypyridine succinate in psoriasis treatment in conditions of formed essential hypertension is also stipulated by high safety level of this drug. Adverse reactions are rare and appear only in form of nausea, dry mouth, sleepiness, excitation or skin allergic reactions and risk of any serious complications development is absent if this drug is used. Moreover, 2-ethyl-6-methyl-3-hydroxypyridine succinate has the minimum potential to interact with other drugs that permits to use it safely in conditions of combined therapy with other drugs of immuno- vaso- and cardiotropic type of action.

Thus, in case of patients with psoriasis and essential hypertension 2-ethyl-6-methyl-3-hydroxypyridine succinate therapy stimulated the reliable decrease of free-radical oxidation intensification signs, in particular, nitrosative (reliable decrease of nitrotyrosine) and oxidative (negative dynamics of endothelin-1 and positive dynamics relative to glutathione metabolism) stresses. In its turn it decreased evidence of apoptotic and inflammatory processes (caspase-8 and TNF-α regress) both directly and indirectly by means of mediating anti-inflammatory effect on endothelium cells and macrophages of anti-coagulant proteinase through endothelial protein C receptor (EPCR) with production of extracellular matrix components and structures and disturbance of microcirculation.

Thus, it determines the key pathogenetic aspects of PS development. Also the decrease of VEGF indicators expression level (regulator of microcirculation vessel formation) and serotonin, associated with this combined therapy, had stipulated statistically significant positive clinical and subjective effects in form of dermatological changes regress (PASI index), decrease of itch (optimization of serotonin biosynthesis and reduction of methionine conversion (with homocysteine formation)) and improvement of life quality.

Talking into account potential influence of 2-ethyl-6-methyl-3-hydroxypyridine succinate on the mentioned pathophysiological predictors and pathogenesis links which to some extent are involved during formation or progress of psoriasis, the use of 2-ethyl-6-methyl-3-hydroxypyridine succinate is rather perspective for psoriasis therapy optimization. Obtained facts and available argumentation of this therapy strategy in literature open new possibilities for use of antioxidants and potential ways for realization of their positive effect in case of PS, especially combined with EH.

Conclusions

1. With initial comparability of key oxidative parameters in both groups after the complex drug therapy there were noticed more evident and reliable positive differences of final values of oxidative stress markers. The values of oxidation markers (oxidated glutathione and nitrotyrosine) in subgroup of the standard therapy without 2-ethyl-6-methyl-3-hydroxypyridine succinate in one month were 2.5 times ($p<0.05$) higher and by 1/3 ($p>0.05$) higher than in the group with added 2-ethyl-6-methyl-3-hydroxypyridine succinate. It was accompanied also by activation of protective antioxidative systems – differences of superoxide dismutase blood serum concentration values after treatment increased by 148.75 % in the group with combined treatment ($p>0.05$) and nearly by 6 % with the traditional therapy.

2. Use of 2-ethyl-6-methyl-3-hydroxypyridine succinate for patients with psoriasis significantly increases effectiveness of the therapy that is shown by higher PASI 75 indicator; in the main group it appears higher than in the control one ($\chi^2=9.87$ if $p<0.05$) and also it improves life quality that is shown by decrease in DLQI indicators.

3. Combined therapy caused the maximum decrease in markers of cytokine activation and apoptosis, improvement of tryptophan and methionine metabolism and also normalization of the cell relations and microvascular processes according to dynamics of these pathological processes markers in parallel downward trend apoptosis marker.

4. Results of additional treatment with antioxidants indicate the high clinical efficiency of 2-ethyl-6-methyl-3-hydroxypyridine succinate combined with traditional therapy.

Perspective goal is assessment of the late results of psoriasis treatment associated with use of 2-ethyl-6-methyl-3-hydroxypyridine succinate.

Conflicts of Interest: authors have no conflict of interest to declare.

References

1. (2014) Cardiovascular psoriasis comorbidities, treatment with atorvastatin. J. *of the American Academy of Dermatology,* 70(1), 165–175.
2. Yeung, H., Takeshita, J, Mehta, N. N., Kimmel, S. E., Ogdie, A., Margolis, D. J., et al. (2013) Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol*, 149(10), 1173–1179. doi: 10.1001/jamadermatol.2013.5015.
3. Sunitha, S., Rajappa, M., Thappa, D. M., Chandrashekar, L., Munisamy, M., & Revathy, G. (2016) Is the Ratio of Antibodies Against Oxidized LDL to Oxidized LDL an Indicator of Cardiovascular Risk in Psoriasis? *OmanMed J.*, 31(5), 390–393. doi: 10.5001/omj.2016.78.
4. Peluso, I., Cavaliere, A., & Palmery, M. (2016) Plasma total antioxidant capacity and peroxidation biomarkers in psoriasis. *J BiomedSci*, 23(1), 52. doi: 10.1186/s12929-016-0268-x.
5. Gu, X., Nylander, E., Coates, P. J., & Nylander, K. (2015) Oxidation reductionis a key process for successful treatment of psoriasis by narrow-band UVB phototherapy. *ActaDermVenereol*, №95(2), 140–146. doi: 10.2340/00015555-1905.
6. Karbach, S., Croxford, A. L., Oelze, M., Schüler, R., Minwegen, D., Wegner, J., et al. (2014) Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. *Arterioscler ThrombVascBiol,* 34(12), 2658–2668. doi:10.1161/ATVBAHA.114.304108.
7. Candel, S. de Oliveira, S., López-Muñoz, A., García-Moreno, D., Espín-Palazón, R., Tyrkalska, S. D., et al. (2014) Tnfa signaling through tnfr2 protects skin against oxidative stress-induced inflammation. *PLoSBiol,* 12(5), e1001855. doi: 10.1371/journal.pbio.1001855.
8. Borska, L., Andrys, C., Krejsek, J., Palicka, V., Chmelarova, M., Hamakova, K. et al. (2014) Oxidative damage to nucleic acids and benzo(a)pyrene-7,8-diol-9,10-epoxide-DNA adducts and chromosomal aberration in children with psoriasis repeatedly exposed to crude coal tar ointment and UV radiation. *OxidMedCellLongev*, 2014, 302528. http://dx.doi.org/10.1155/2014/302528.
9. Prussick, R., Prussick, L., & Gutman, J. (2013) Psoriasis Improvement in Patients Using Glutathione-enhancing, Nondenatured Whey Protein Isolate: A Pilot Study. *J Clin Aesthet Dermatol*, 6(10), 23–26.
10. Kothiwala, S. K., Khanna, N., Tandon, N., Naik, N., Sharma, V. K., Sharma, S., & Sreenivas, V. (2016) Prevalence of metabolic syndrome and cardiovascular changes in patients with chronic plaque psoriasis and their correlation with disease severity: A hospital-basedcross-sectional study. *Indian J Dermatol Venereol Leprol,* 82(5), 510–518. doi: 10.4103/0378-6323.183638.
11. Yeung, H., Takeshita, J., Mehtaetal, N. N., Kimmel, S. E., Ogdie, A., Margolis, D. J., et al. (2013) Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol*, 149(10), 1173–9. doi: 10.1001/jamadermatol.2013.5015.
12. Menter, A. (2016) Psoriasis and psoriatic arthritis overview. *Am J Manag Care,* 22(8), 216–224.
13. Cea-Calvo, L., Vanaclocha, F., Belinchónetal, I., Rincón, Ó., Juliá, B., Puig, L. (2016) Under diagnosis of Cardiovascular Risk Factors in Out patients with Psoriasis Followedat Hospital Dermatology Offices: The PSO-RISK Study. *Acta Derm Venereol,* 2016. doi: 10.2340/00015555-2434.
14. Ganzetti, G., Campanati, A., Molinelli, E., & Offidani, A. et al (2016) Psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease: Three different diseases on a unique background. *World J Cardiol*, 8(2), 120–131. doi: 10.4330/wjc.v8.i2.120.
15. Egeberg, A., Khalid, U., Gislason, G. H., Mallbris, L., Skov, L., Hansen, P. R. (2016) Impact of Depression on Risk of Myocardial Infarction, Stroke and Cardiovascular Deathin Patients with Psoriasis: A Danish Nationwide Study. *Acta Derm Venereol*., 96(2), 218–221. doi: 10.2340/00015555-2218.
16. Machado-Pinto, J., Diniz Mdos, S., & Bavoso, N. C. (2016) Machado-Pinto J. Psoriasis: new comorbidities. *An Bras Dermatol*, 91(1), 8–14. doi: 10.1590/abd1806-4841.20164169.

17. De Vecchis, R., Baldi C., & Palmisani, L. (2016) Protective effects of methotrexate against ischemic cardiovascular disorders in patients treated for rheumatoid arthritis or psoriasis: novel therapeuticin sights coming from a meta-analysis of the literature data. *Anatol J Cardiol*., 16(1), 2–9. doi: 10.5152/akd.2015.6136.
18. Reich, K., Mrowietz, U., Radtke, M. A., Thaci, D., Rustenbach, S. J., Spehr, C., & Augustin, M. (2015) Drug safety of systemic treatments for psoriasis: results fromThe German Psoriasis Registry Pso Best. *Arch Dermatol Res*, 307(10), 875–83. doi: 10.1007/s00403-015-1593-8.
19. Tarkin, J. M., & Rudd, J. H. (2015) Psoriasis: More Than Just Skin Deep. *Arterioscler Thromb Vasc Biol*, 35(12), 2487–2488. doi: 10.1161/ATVBAHA.115.306560.

Information about authors:
Vizir V. A., MD, PhD, DSci, Professor, Head of the Department of Internal Diseases 2, Zaporizhzhia State Medical University, Ukraine.
Makurina G. I., MD, PhD, Associate Professor, Department of Dermatovenerology and Cosmetology with the Course of Dermatovenerology and Aesthetic Medicine of the Postgraduate Education Faculty, Zaporizhzhia State Medical University, Ukraine, E-mail: makurina.g@yandex.ua.
Відомості про авторів:
Візір В. А., д-р мед. наук, професор, зав. каф. внутрішніх хвороб 2, Запорізький державний медичний університет, Україна.
Макуріна Г. І., канд. мед. наук, доцент каф. дерматовенерології та косметології з курсом дерматовенерології і естетичної медицини ФПО, Запорізький державний медичний університет, Україна, E-mail: makurina.g@yandex.ua.
Сведения об авторах:
Визир В. А., д-р мед. наук, профессор, зав. каф. внутренних болезней 2, Запорожский государственный медицинский университет, Украина.
Макурина Г. И., канд. мед. наук, доцент каф. дерматовенерологии и косметологии с курсом дерматовенерологии и эстетической медицины ФПО, Запорожский государственный медицинский университет, Украина, E-mail: makurina.g@yandex.ua.

Поступила в редакцию 03.10.2016 г.