



Experimental and clinical study of the efficacy of medicines containing omega-3 and 6 polyunsaturated fatty acids, in the treatment of inflammatory skin diseases

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Abstract

Introduction: Over the recent years, the attention of scientists regarding the search for alternative means of treatment, including local therapy, of inflammatory skin diseases, has been focused in recent years on medicines containing omega-3 and 6 polyunsaturated fatty acids (PUFA).

Objectives: to substantiate the feasibility of using medicines containing omega-3 and 6 polyunsaturated fatty acids and antioxidants in the treatment of inflammatory skin diseases.

Methods: The studies were carried out on 224 conventional white rats of the Wistar line in compliance with the international principles of the European Convention for the Protection of Vertebrates. A burn injury was used to cause experimental simple irritant contact dermatitis. After trying various treatment options with using Omegaven, histopathological examinations of 18 fragments of affected skin of white rats with cross sections stained with hematoxylin–eosin and pikrofuxin by Van Gieson’s method. The state of lipid peroxidation (LPO) in blood and affected skin was evaluated in the animals. One hundred forty-six patients with inflammatory skin diseases (dermatitis simple irritant contact, allergic contact dermatitis, atopic dermatitis, neurodermatitis, psoriasis, cutaneous mastocytosis in children) were observed. In treatment, there were used medicines with omega-3 and 6 PUFA or an antioxidant medicines.

Results and discussion: Skin reactions of dermatitis simple irritant contact in rats after burn injury were evaluated at different points of time. The observations showed higher efficacy of medicines containing PUFA than standard anti-inflammatory agents in the treatment of simple irritant contact dermatitis. Histopathological examination of the skin of white rats with simple irritant contact dermatitis after the 11-day treatment revealed that the expression and composition of the cellular reaction in the lesions with a predominating lymphocytes and macrophages (mainly cell response) differ significantly from those treated with Radevit ointment (segmented neutrophil leukocytes, eosinophils – delay in the acute phase of inflammation). There was identified a smaller thickness (up to 1/3) of the strips of granulation tissue under the actively proliferating cells of the epidermis. It was possible to demonstrate the superiority with respect to reducing the activity of LPO medicines containing omega-3 and 6 PUFA, over those with anti-inflammatory action. The clinical observations of patients showed high efficacy of the local treatment with medicines containing omega-3 and 6 PUFA, or antioxidant.

Conclusion: For the first time, the mechanism of implementing an anti-inflammatory effect of the experimental medicines containing omega-3 and 6 polyunsaturated fatty acids (Omegaven, Vitamin F99 cream rich), – an antioxidant effect - when treating simple irritant contact dermatitis when treating simple irritant contact dermatitis; that is the weakening of the severity of oxidative stress. For the first time, the greatest contribution of an increased activity of catalase to the weakening of oxidative stress in the affected skin is shown.

Keywords

skin, inflammation, polyunsaturated fatty acids, treatment.

Introduction

Improvement of local and systemic treatment of chronic skin diseases, including those with a significant pathogenetic role of inflammatory reactions, is a highly urgent task at the moment (Kubanova and Akimov 2009). At the same time, alternative therapies are gaining momentum. A widespread and prolonged external use of corticosteroids to treat dermatitis can cause a number of negative effects: atrophy of the skin and subcutaneous adipose tissue, telangiectasia, hypertrichosis, erythroderma, etc. In recent years, the attention of researchers in the systemic and local treatment has been attracted to medicines containing omega-3 and omega-6 polyunsaturated fatty acids and antioxidants (Kasichina 2015).

The term Vitamin F refers to the complex of fatty acids: linoleic, linolenic, arachidonic and their esters in Russian and foreign scientific literature. Among the tools of systemic therapy, the following ones containing polyunsaturated fatty acids were used: Alkanol, fish oil, eicosapentaenoic and docosahexaenoic acids, Polyene antioxidant capsules, Eikovit capsules, biologically active supplement “Norvesol”, Eslidin capsules (Smirnov 2009, Kremer et al. 1995). As for the medicines of external use containing omega-3 and omega-6 PUFA, the authors used ointment containing 20 % PUFA with 0.5% antiseptic Dioxin to treat wounds and burns. Medicines containing vitamin F are Linetol and Eikonol. The composition of Eikovit gel includes internal fat of whitefish and salmon fish, containing PUFA, alpha-tocopherol, vitamins A, K with the action of anti-inflammatory, antioxidant, and wound healing effects. Omega-3 and 6 PUFA are contained in dermatologic medicines made by Uriage company (Xemose Universal Emollient Cream and Pruriced Cream).

Simple irritant contact dermatitis, allergic contact dermatitis, atopic dermatitis, neurodermatitis (focal and diffuse), psoriasis, urticaria pigmentation (ICD-10) are inflammatory skin diseases (Hehbif 2006). The diseases can be acute (simple irritant contact dermatitis, allergic contact dermatitis), or chronic (atopic dermatitis, neurodermatitis, psoriasis, skin forms of mastocytosis in children). Acute inflammation, such as burns, can cause mild tissue damage, and chronic inflammation significantly affects the functioning of the skin (Kasihina 2015).

Simple irritant contact dermatitis is a classic inflammatory skin disease, in which the acute phase is accompanied by erythema, vesiculation and itching. This skin inflammation is caused by contact with a damaging agent, such as, physical and thermal trauma, etc. (Kasihina 2015, Skripkin and Mordovtsev 1999).

The efficacy was noted when using a complex treatment of dermatitis, eczema, psoriasis and other skin diseases by means of medicines containing omega-3 and 6 PUFA (Ziboh 1989).

By the moment, a medicine for parenteral infusion containing PUFA has been developed – Omegaven emulsion. The indications for its use are: septicemia, thermal and chemical burns. Its pharmacological action: making up for the deficiency of polyunsaturated fatty acids (Gostishchev et al. 2011, Gostishchev and Kosinets 2012a, Vyshkovskii 2016).

In the available scientific literature, there has been found no information on an experimental study on the model of simple irritant contact dermatitis if the effects of the systemic therapy by means of omega-3 and 6 PUFA, as well as by Vitamin F99 cream rich, including similar components. Neither has been covered the issue of a comparative study of the action of these medicines and Radevit ointment, which is officially recommended to treat simple irritant contact dermatitis, on the intensity of skin inflammatory reactions. There is no literature data on the state of lipid peroxidation (LPO) in blood and affected skin of experimental animals in such a study. That was the reason to use it in the experiments the present study is based on. Regarding the clinical phase of work, it concerned a local therapy to treat simple irritant contact dermatitis, allergic contact dermatitis, atopic dermatitis in children, focal and diffuse neurodermatitis, psoriasis, cutaneous forms of mastocytosis in children (inflammatory skin disease) with medicines containing omega-3 and 6 polyunsaturated fatty acids (Pruriced Cream, Xemose Universal Emollient Cream) or by thermal water by Uriage with the antioxidant, anti-inflammatory and skin hydrating effects (Bariederm Cream, Pruriced Gel, Cu-Zn cream, gel, spray, Keratosane-15 Lait-cream). No publications on the evaluation of either efficacy or safety of applying the above medicines in the local therapy to treat inflammatory skin diseases.

LPO and antioxidant system (AOS) are in close connection with inflammatory skin reactions. Free radicals constantly form during oxidation-reduction reactions: reactive oxygen species (superoxide-anion, singlet oxygen form, hydroxyl radical, hydrogen peroxide), radicals which form during LPO (lipoperoxides), oxidized halogens (chloramine, hypochlorite), and nitrogen oxide. Normally, LPO maintains the vitality of the body, participating in the protective (phagocytosis) and regulatory functions. The intensity of LPO processes in physiological conditions is regulated by a multi-stage complex system of AOS – enzymatic (specific) and non-enzymatic (non-specific) links. The system ensures the preservation and maintenance of the steady state of free radical processes (Dreev et al. 1991, Rumley and Paterson 1998, Knight 2000).

Superoxide dismutase (SOD), catalase (CAT) and glutathione S-transferase are the main components of the LPO. The system enables free-radical processes to proceed at the optimal level (Winterbourn 1989). As for the AOS-protection in skin, the system mainly consists of the enzymes: CAT, SOD, glutathione peroxidase (Ketsa and Shved 2014, Fridovich 1983, Ghadially et al. 1996, Byczkowski and Gessner 1998, Ratnam et al. 2006).

Purpose of research

In the experiment, to substantiate and clinically confirm the feasibility of using PUFA medicines and antioxidants in the treatment of inflammatory skin diseases.

Methods

The studies were carried out on 224 inbred conventional white Wistar rats aged 3-6 months weighing 300-350 g in compliance with the international principles of the European Convention for the Protection of Vertebrates, taking into account the rules of biomedical ethics (with the permission of Rostov Ethics Committee, Protocol No. 16/13 dated 14.11.2013) (Karkichenko N.N., Grachev S. V., 2010). A burn injury was caused by a circular metal plate with an area of 3.8 cm², 1.5 mm thick, and the contact with the skin was 3 seconds. The plate was heated in two ways: on a spiral-covered electric stove at the initial signs of redness of the metal part covering the spiral (pronounced burn injury, 200 degrees C) and after a 20-second cooling on a metal plate of the room temperature (moderate burn injury, 120 degrees C).

Omegaven was injected into the abdomen of white rats at a dose of 3.0 ml/kg daily in the form of emulsion for infusion, and Radevit ointment and Vitamin F99 cream rich were also applied daily to the lesions with swabs. For the prevention of pyoderma, once every 3 days, Erythromycin ointment was applied onto the foci. During the experiment, the recommendations of the International Contact Dermatitis Research Group were modified (Ka-

mbas and Lotti 2008). The reaction was estimated as a sharply positive (3+), if the thickness of the edematous infiltrate was 3 mm or more, positive (2+) with edematous infiltrate from 1 to 2 mm, or weakly positive reaction (1+) – with the infiltrate thickness of 1 mm or less. The corrective coefficient for 3+ was 1.0, for 2+ – 0.66, and for 1 – 0.33. The half sum of the two orthogonal diameters or the area of the inflamed lesion was multiplied by a corrective coefficient, obtaining an indicator in corrected diameter units (CDU) or corrected area units (CAU) (Grebennikov et al. 1978). There were the following groups of animals: control group (without simple irritant contact dermatitis), group 1.1 (simple irritant contact dermatitis 4 days without treatment), group 1.2 (simple irritant contact dermatitis 11 days without treatment), group 2 (On the second day after the burn, Radevit ointment was applied onto the foci. Radevit ointment is an officially recommended anti-inflammatory medicine for the treatment of simple irritant contact dermatitis.), group 3 (The animals of the 3rd group received two manipulations daily for 11 days: injections of Omegaven emulsion into the abdominal cavity, as well as application of Vitamin F99 cream rich onto the foci.), group 4 (the animals were treated only with Vitamin F99 cream rich). The main active ingredient of Omegaven is highly purified fish oil, containing PUFA.

In the available scientific literature, there have been no reports found on the effect of Omegaven on the inflammatory reaction of the skin. However, it is the only drug containing PUFA for parenteral administration. Thus, it explains the novelty of the present research.

Vitamin F99 cream rich (Research Laboratory Strelets Ltd, Russia) includes vitamin F as a source of essential polyunsaturated fatty acids and esters of omega-3 fatty acids. Radevit ointment (Retinoids, Russia), with anti-inflammatory action, applied in group 2, enhances the protective function of the skin. The indications include burns, allergic contact dermatitis, and inflammatory skin diseases.

Histopathological examinations of 18 fragments of affected skin of the experimental white rats with further staining the cross sections with hematoxylin–eosin and pikrofluxin by Van Gieson's method. The AOS state in blood and skin extracts was assessed by determining the content of Malondialdehyde (Stalnaya and Garishvili 1977), the activity of superoxide dismutase (Mitra and Fridovich 1972) and of catalase (Korolyuk et al. 1988).

In the clinical studies to evaluate the effectiveness of local therapy that contains omega-3 and 6 PUFA, with either antioxidant, anti-inflammatory, or skin hydrating effects, 146 patients were observed with inflammatory diseases of the skin, 44% males and 56% females, aged from 2 months to 83 years. Among them, 22 patients were diagnosed with simple irritant contact dermatitis, 32 patients – with allergic contact dermatitis, 28 children – with atopic dermatitis, 13 patients – with neurodermatitis (focal and diffuse), 28 patients – with psoriasis, and 23 children – with a cutaneous form of mastocytosis. Assessment of the severity of atopic dermatitis – SCORAD, and

a PASI index applied in the study is the basic standard for assessing the severity of psoriasis. Family Dermatology Life Quality Index (FDLQI) and HAM (health-activity-mood) index were used to assess a psychological state of patients with dermatoses.

The obtained data were processed by the method of variation statistics and calculation of arithmetic mean values (M) and errors of average values (m). The significance was evaluated by Student's criterion (t), and differences were considered reliable at the probability level of more than 95% ($P < 0.05$).

Results and discussion

Skin reactions (simple irritant contact dermatitis) after a burn injury were evaluated after 1 day, and then after 4 days, 7 days, and 11 days (Table 1). After this period, the manifestations of simple irritant contact dermatitis in most animals were insignificant.

In severe burn injury in rats of group 1.2 after 4 days without treatment, the indicators were 22.85 ± 0.43 CDU and 4.12 ± 0.15 CAU. The observation in group 3 with simple irritant contact dermatitis treated by a combination of Omegaven injection and, externally, Vitamin F99 cream rich showed consistent dynamics with a 1.15-time increased inflammatory reaction of the skin from day 1 to day 4 ($P < 0.05$ in terms of the corrected area). Further, under the influence of treatment, by day 7 the skin reaction became 1.5-time weaker than that after 4 days according to the average corrected diameter and corrected area ($P < 0.001$). The manifestations of simple irritant contact dermatitis were significantly weakened by day 11 of treatment: they were 2.5-time ($P < 0.001$) less intense and 3-time ($P < 0.001$) less intense than after 4 days, and when compared with the indicators after 7 days, 1.7 times and 2 times ($P < 0.001$), respectively.

The comparison of group 3 indicators (7 days) and groups 3 (11 days) with those in groups 2 (7 days) and 2 (11 days) showed in group 3 after 7 days of treatment 1.2-time less pronounced inflammatory reactions of the skin ($P < 0.05$) and by 1.25 times ($P < 0.05$). In the same group 3 after 11 days of treatment, the intensity of inflammatory skin reactions was 1.8-time ($P < 0.001$) and 2.5-time ($P < 0.001$) lower than in group 2 (11 days). This demonstrates the advantage of complex anti-inflammatory treatment with Omegaven and Vitamin F99 cream rich

compared to that with Radevit ointment. The advantage increased by day 11.

After 7 days of observation in group 3, the indicators were 1.5-time lower than those in group 3 (4 days) - more convincing than in group 2 for the 7 days of observation - significantly (1.2 times).

The severity of simple irritant contact dermatitis in group 3 (7 days) was less than in group 2 (7 days). After 11 days of treatment, the indicators of group 3 were 1.8-time ($P < 0.001$) and 2.15-time ($P < 0.001$) lower than those in group 2 (11 days), that is, treatment by day 7 and day 11 was more effective in group 3 than in group 2.

Eleven days after the development of simple irritant contact dermatitis, the indicator of the group without treatment (group 1.2) exceeded ($P < 0.05$) that 1.2 times with an estimate of the corrected diameter when using the treatment with Radevit (group 2), and 2.1 times when using treatment with Omegaven and Vitamin F99 cream rich (group 3) and 1.4 times when compared with group 4. A similar pattern was noted when assessing by means of corrected area units.

The indicators of group 3 were significantly less than those in groups 3 (4 days) and 3 (7 days), and also those in group 2 (11 days) treated with Radevit ointment - 1.8 times ($P < 0.001$) and 2.2 times ($P < 0.001$) after 11 days of treatment of simple irritant contact dermatitis in white rats. A similar pattern was revealed when comparing the indicators of group 3 (11 days) and 4 (11 days). Group 3 indicators (11 days) were 1.5-time ($P < 0.001$) and 1.7-time ($P < 0.001$) less pronounced. Thus, the higher efficiency is obvious when treating simple irritant contact dermatitis with Omegaven and Vitamin F99 cream rich than when treating it with Radevit ointment and Vitamin F99 cream rich. When making an experiment with simple irritant contact dermatitis after a moderate burn injury, all the above mentioned regularities of the dynamics of the simple irritant contact dermatitis under the influence of different 3-treatment options repeated.

The observations showed higher efficiency of medicines containing PUFA (Omegaven, Vitamin F99 cream rich) than Radevit ointment of group 2, in the treatment of simple irritant contact dermatitis in experimental white rats. The combination of Omegaven and Vitamin F99 cream rich for an anti-inflammatory effect on the foci of simple irritant contact dermatitis was more significant than the action of only Vitamin F99 cream rich.

Table 1. Skin reactions in simple irritant contact dermatitis (severe burn injury) in corrected diameter units

Groups of experimental white rats (n = 20)	Severity of simple irritant contact dermatitis at different periods after burn			
	After 1 day, CDU	After 4 days, CDU	After 7 days, CDU	After 11 days, CDU
Group 1.2 – simple irritant contact dermatitis, 11 days without treatment	21.30±0.39	22.85±0.43, 2*	22.20±0.61, 4*	19.70±0.52*, 4*
Group 2 –Radevit ointment	20.09±0.92	21.90±0.86	19.04±0.60*, 4*	16.60±0.44*, 3*, 4*
Group 3 –Omegaven&Vitamin F99 cream rich	22.42±0.92	23.20±0.22	15.59±0.49*, 3*	9.20±0.56*, 3*
Group 4 –Vitamin F99 cream rich	22.07±0.55	24.50±0.38*	16.68±0.63*, 3*	14.07±0.21*, 3*, 4*

Note. The differences are significant ($P < 0.05$): with group 1.2 (4 days) - *, with an indicator of "its own" group (1 day) - 2*, with an indicator of "its own" group (4 days) - 3*, with indicators of group 3 after 7 or 11 days, respectively, - 4*. The reliability of other comparisons is given in the text.

The histopathological examination of the skin of white rats with simple irritant contact dermatitis after 11-day treatment with Omegaven injections into the abdominal cavity and with external use of Vitamin F99 cream rich allowed to note less pronounced infiltrates and a different cell reaction in the foci with predominating lymphocytes and macrophages than in those treated with Radevit ointment (neutrophil segmentonuclear leukocytes, eosinophils – delay of the acute phase of inflammation). A smaller thickness (up to 1/3) of a granulation tissue strip under the actively proliferating epidermal cells was also revealed. This will probably lead to the formation of a more delicate scar. There was a more pronounced anti-inflammatory effect in experimental treating simple irritant contact dermatitis with Omegaven injections into the abdominal cavity and external use of Vitamin F99 cream rich compared to those treated with Radevit ointment.

There is a close connection between PUFA and AOS in the body. It was found that omega-3 PUFA have an antioxidant effect (Ketsa, Shved and Petrik,2014). According to (Shepeleva. and Shovkun 2012), through the stage of PUFA derivatives occurs the biosynthesis of prostaglandins (PG) and leukotrienes (LT).

Among the final AOS products Malondialdehyde (MDA) plays the leading role in the formation of complexes, and the antioxidant protection system in the skin includes mainly antioxidant enzymes SOD, CAT, etc.

The MDA content, the activity of SOD and CAT were evaluated in the blood of white rats with severe burn injury in different treatments (Table 2).

In group 3 of white rats (they received 2 medicines that contain omega-3 and 6 PUFA) after 11 days of therapy, the MDA rate was higher than the control and 1.1 groups (in group 2 after treatment with Radevit ointment, the MDA rate was 1.4- and 1.3-time higher than that in the control and 1.1 groups, respectively). The activity of blood SOD was 2.8-time higher than that in group 1.1 (simple irritant contact dermatitis without treatment – 4 days), and CAT was 1.5 times higher. The tables show that the comparison of blood LPO group 1.2 (simple irritant contact dermatitis without treatment –11 days) and group 3 (combined treatment with Omegaven and Vitamin F99 cream rich – 11 days) revealed less pronounced activation of LPO in group 3 and, on the contrary, the prevailing activity of SOD and CAT.

Particular attention is drawn to the excess of CAT activity in group 3 compared to group 2 (Radevit ointment treatment) by 1.3 times. For all 3 studied components of LPO and AOS, the indices of the 3rd group were more favorable than in the 2nd group. Thus, the treatment of dermatitis simple irritable contact with medicines containing omega-3 and 6 PUFA (Omegaven, Cream “Vitamin F99” rich), was more effective than the anti-inflammatory activity of Radevit ointment.

In experimental dermatitis simple irritable contact in white rats oxidative stress was noted. There is AOS decompensation which remained until significant clinical stabilization in the foci of severe burn injury. The most effective in relation to the state of AOS was a combination of Omegaven and Cream “Vitamin F99” rich. So it was possible to demonstrate the superiority with respect to the activity of AOS medicines containing omega-3 and 6 PUFA, over medicines of anti-inflammatory action (Radevit ointment).

We found it advisable to evaluate the content of MDA in the affected skin from the foci of inflammation, as well as the activity of SOD and CAT in the process of local treatment using the following means: Radevit ointment anti-inflammatory action, as well as Cream “Vitamin F99” rich Containing omega-3 and 6 PUFA (the most pronounced beneficial effect on the state of the blood AOS of the combination of injections of Omegaven and externally Cream “Vitamin F99” rich has already been convincingly demonstrated above).

The experiments were conducted in parallel with severe burn injury (experiment 1) and with moderate burn injury (experiment 2). The results are presented in Tables 3 and 4.

The content of MDA 4 days after a severe burn injury (without treatment) increased sharply (147.9±4.4 nmol/g – 2.3 times; P<0.01). The indices of experiments 1 exceeded 1.4 times those of experiment 2 (P<0.05). The reason was the difference in the severity of burn injury.

Clear dynamics in all 3 groups of treatment in both variants of the experiment was shown by the activity of CAT of the affected skin, which significantly increased. In a severe burn injury, CAT activity increased 1.5 times in group 1.1 (P<0.001), 1.5 times in group 2 (P<0.001), 1.7 times in group 4 (P<0.001). Accordingly, with a moderate burn injury, CAT activity increased 1.7 times in group 1.1 (P<0.001), and 1.5 times in groups 2 and 4 (P<0.001).

Table 2. Components of the antioxidant system of blood of rats with simple irritant contact dermatitis (severe burn injury)

Groups of experimental white rats (n = 20)	MDA [nmol/ml]	SOD [RU/ml]	CAT [U/ml x min]
Control group – without simple irritant contact dermatitis	6.23 ±0.26	23.83±0.94	44.31±1.81
Group 1.1 – simple irritant contact dermatitis, 4 days without treatment	7.06±0.26*, 3*	11.81±0.57*, 3*, 4*, 5*	33.55±0.75*
Group 1.2 – simple irritant contact dermatitis, 11 days without treatment	10.30±0.25*, 2*, 4*, 5*	15.79±1.01*, 2*, 4*, 5*	35.00±1.46*, 5*
Group 2 – Radevit ointment – 11 days	8.80±0.24*, 2*, 3*	32.30±3.18, 2*, 3*	38.60±0.47*, 2*, 5*
Group 3 – Omegaven&Vitamin F99 cream rich – 11 days	7.88±0.28*, 3*	33.42±3.11, 2*, 3*	48.60±1.17*, 2*, 3*, 4*

Note. Significant differences (p<0.05): with control group - *; with group 1.1 – without treatment 4 days –2*; with group 1.2 – without treatment 11 days –3*; with group 2 – 4*, with group 3 – 5*. The reliability of other comparisons is given in the text.

Table 3. LPO system indicators of the affected skin of white rats with simple irritant contact dermatitis (“severe burn injury”)

Groups of white rats (n = 20)	MDA [nmol/ml]	SOD [RU/ml]	CAT [U/ml x min]
Group control – without simple irritant contact dermatitis	63.15±4.44	589.6±26.7	20.50±1.26
Group 1.1 – simple irritant contact dermatitis, 4 days without treatment	147.9±4.4*, 3*	453.0±32.1*	30.84±0.86*, 3*
Group 1.2 – simple irritant contact dermatitis, 11 days without treatment	171.3±4.0*, 2*	459.9±15.3*, 6*	25.30±0.54*, 2*, 4*, 6*
Group 2 – Radevit ointment, 11 days	164.1±6.3*	470.1 ±41.8*	30.49±0.97*, 3*
Group 4 – Vitamin F99 cream rich, 11 days	142.6±8.0*, 4*	597.6±14.6, 2*, 3*	33.92±0.67*, 3*, 4*

Note. Differences are significant (p<0.05): with control group – *, with group 1.1 without treatment 4 days after burn injury – 2*, with group 1.2 without treatment 11 days – 3*. The reliability of other comparisons is given in the text.

Table 4. LPO indicators of affected skin of white rats with simple irritant contact dermatitis (“moderate burn injury”)

Groups of white rats (n=20)	MDA [nmol/ml]	SOD [RU/ml]	CAT [U/ml x min]
Group control – without simple irritant contact dermatitis	63.15±5.0	589.6±31.7	20.50±1.49
Group 1.1 – simple irritant contact dermatitis, 4 days without treatment	107.4±11.2*, 3*	468.2±69.4	33.78±1.70*, 3*
Group 1.2 – simple irritant contact dermatitis, 11 days without treatment	148.8±14.1*, 2*	493.3±30.8	24.75±1.93, 2*
Group 2 – Radevit ointment 11 days	113.2±24.6	531.6±95.1	30.92±1.03*, 3*
Group 4 – Vitamin F99 cream rich 11 days	139.6 ±16.3*	682.2±44.7, 2*, 3*	29.90 ± 1.80*

Note. Differences are significant (P<0.05): with control group – *; with group 1.1 without treatment 4 days after burn injury – 2*; with group 1.2 without treatment 11 days – 3*. The reliability of other comparisons is given in the text.

Much less definite in both versions of the experiment was the activity of SOD. In groups 1.1 in both variants of the experiment in terms of the indicators of MDA and SOD, there was found out, decompensation of the LPO and AOS systems (oxidative stress), according to the indicators of CAT of the affected skin, the signs of compensation of these systems were revealed.

In both variants of the experiment in 4 groups compared with groups 1.1, the activity of SOD was 1.3 times and by 1.5 times higher, respectively. Thus, the reliable compensation of AOS was established due to a relatively increased activity of SOD in 4 groups in addition to an increased activity of CAT of the affected skin – 1.7 times in the group with a severe burn injury and 1.5 times in the second version of the experiment. There was no such a favorable dynamics of the leading components of the LPO in group 2. The comparison of LPO indicators in the affected skin in group 1.2 (11 days without treatment) and group 4 (treatment with Vitamin F99 cream rich) revealed prevalent activity of SOD and CAT in group 4 with severe and moderate burn injuries.

The analysis of interrelation between LPO and AOS in blood and affected skin with simple irritant contact dermatitis in the experimental white rats revealed certain patterns in different methods of treatment. In the study of blood, the most effective in relation to the LPO and AOS states was the treatment with a combination of Omegaven and Vitamin F99 cream rich.

By the 4th day after a severe burn injury (without treatment), there was recorded decompensation in the LPO blood system – oxidative stress. With the continuing inflammatory reaction of the skin in the foci of simple irritant contact dermatitis, although significantly reduced

after 11 days of treatment, along with signs of oxidative stress (increased MDA), there were clear manifestations of compensation of the LPO system (relative increase in the activity of SOD and CAT of blood).

The data obtained justify the use of external and systemic medicines containing omega-3 and 6 PUFA, as well as antioxidants in the treatment of skin diseases with an inflammatory component of pathogenesis (simple irritant contact dermatitis, allergic contact dermatitis, atopic dermatitis, neurodermatitis, psoriasis, skin form of mastocytosis in children). The period of using PUFA and antioxidants is from the exacerbation of skin diseases and further to rashes with the weakening of the signs of inflammatory reaction of the affected skin – erythema, swelling, infiltration, and itching.

The authors together with a group of dermatologists participated in the treatment, assessment of the severity of diseases, analysis of the dynamics of symptoms, the results of treatment, including long-term ones, using together local therapeutic agents omega-3 and 6 PUFA, as well as thermal water Uriage with antioxidant, anti-inflammatory, and skin hydrating effects. Systemic treatment was traditional in accordance with modern Federal clinical guidelines on dermatology (Russian Federation) (Kubanova 2016). Omega-3 and 6 PUFA were administered topically in form of Pruriced Cream and Xemose Universal Emollient Cream, and thermal water Uriage was prescribed in in form of Bariederem Cream, Pruriced gel, Cu-Zn cream, gel, spray, Keratosane-15 Lait-cream (Uriage, France).

There were 2 groups of patients with skin diseases. To treat skin diseases, the patients of the 1st group used Bariederem Cream containing thermal water Uriage. In the 1st

subgroup (1st Group), there were 22 young women who in the winter season had simple irritant contact dermatitis exposed by wind and cold (dry skin, erythema, peeling, cracks). In the morning, 15 minutes after using cosmetic cream, they applied Bariederm Cream to the foci of irritation; if necessary, this was repeated in the 2nd half of the day. All women in this subgroup recovered.

In the 2nd subgroup (1st Group), there were 32 patients with allergic contact dermatitis (12 doctors, 7 hairdressers, 4 housewives exposed to a negative impact of home care products, 9 patients of other professions). Five people had allergic contact dermatitis from exposure to cosmetic products, 4 patients had a skin reaction to dyed fabric in the points of contact with tights or jeans, 3 patients had a skin reaction to metal zippers and buckles. The reactions were mostly erythematous lesions with some swelling, infiltration of the skin, peeling, sometimes with vesicular or crusted elements with itching. The duration of the disease was from 4 weeks to 6 months. In the treatment of allergic contact dermatitis, Advantan was prescribed, and 15 minutes after its application, Bariederm Cream was applied. After 10 days, Advantan was discontinued, and then only Bariederm Cream was used 2-4 times a day. The patients were observed to recover, without any adverse events from treatment. There was recorded no recurrence of allergic contact dermatitis from 2 to 12 in 28 patients (88%), and the disease was in a mild form in 4 cases.

In the 3rd subgroup (1st Group), 23 children under 5 years of age with cutaneous forms of mastocytosis were observed. Thirteen children had bullous form, 5 children had papular form, 5 patients had macular form. The most frequent symptoms were small rounded reddish-brownish spots, or several yellowish-brown swollen papules symmetrically arranged; when rubbing – Darier's symptom. Systemic therapy to stop the activation of skin forms of mastocytosis was supplemented locally with non-steroidal drug Pimecrolimus Cream 1%, selectively inhibiting the synthesis and release of inflammatory mediators by mast cells. Pimecrolimus was applied at the first signs of activation of the elements. Such a treatment quickly reduced or led to a complete regression of the inflammatory response. To prevent the activation of mastocytosis from exogenous trigger factors (friction, atmospheric effects, bathing), in a non-acute phase, Bariederm Cream, protecting skin from aggressive environmental factors, was applied to the areas of rashes in the children twice a day. The treatment reduced the frequency of activation of mastocytosis elements (according to the parents' observations, 7-8-fold). For the period from 4 weeks up to 14 months, no undesirable side effects were found. The results of treatment were regarded as an improvement (which is very important in this disease). Life quality improvement of the sick children's mothers was statistically significant: from 28.00 ± 0.38 to 10.00 ± 0.50 points ($P < 0.001$; FDLQI).

In the 2nd group, there were patients with inflammatory dermatoses, who along with standard systemic therapy used external medicines containing omega-3 and 6 PUFA, or thermal water Uriage.

In the 1st subgroup (2nd Group), there were 13 patients with neurodermatitis (focal and diffuse), the leading symptom of which was persistent intense itching. Focal neurodermatitis was more often localized on the back and sides of the neck, in 3 characteristic zones on ankle joints. With diffuse neurodermatitis, the patients had numerous miliary slightly pink itchy papules, erythema, swelling, infiltration, lichenification in the elbow and knee folds, on the neck, radiocarpal joints, etc. The skin was dry and grayish. Standard systemic therapy was administered in all the patients, and topically – Cream or Pruriced gel – depending on the localization of the lesions on the skin or hairy part of the head, as well as the severity of inflammation. On the first, day positive effect was observed to some extent in 12 people (94%). Two weeks later, itching completely stopped in 6 patients, significantly decreased in 4 and decreased in 3 people. Monitoring of patients for 6 months showed that with the disappearance of itching 9 people stopped applying Pruriced, and the rest continued to use it much less frequently. A high effect of using Pruriced in atopic eczema (focal and diffuse) was also recorded, without the use of topical corticosteroids.

In the 2nd subgroup (2nd group), there were 28 children with atopic dermatitis (mild to moderate form), in treating whom antioxidant, ant-inflammatory, antiseptic agents, such as Cu-Zn cream, gel or spray were used. The age of the sick children varied from 2 to 16 years. Cu-Zn cream or spray (for moist areas; gel-for hygienic procedures) daily 2 times a day on foci in addition to standard systemic therapy was prescribed to 17 children (index SCORAD 49.00 ± 1.5 points), another 11 people (index SCORAD 50.0 ± 2.3 points) received traditional treatment without Cu-Zn cream. The effectiveness of therapy was evaluated after 2 weeks and 6 months. After a 2-weeks treatment of the patients with Cu-Zn cream, SCORAD index decreased ($P < 0.01$) to 23.0 ± 1.4 points, and in the subgroup of comparison – to 29.0 ± 1.6 points (1.3 times higher; $P < 0.05$). Among those who used Cu-Zn cream rashes completely resolved in 4 patients (24%), in the rest there was a significant improvement. In the subgroup of comparison, a significant improvement was in 5 patients (46%), in the rest of the children, there was only improvement. The long-term results were more favorable among those who used Cu-Zn cream in treatment.

In the 3rd subgroup (2nd Group), there were 19 patients with psoriasis with frequent relapses. The majority of the patients had acute dermatosis 3 times a year or more (PASI index on average 29.7 ± 1.1). In addition to standard treatment, including topically external corticosteroids, the patients used Keratosane-15 Lait-cream with 2-3 applications per day. Keratosane-15 Lait-cream contains antioxidant thermal water Uriage. After 2 weeks of the therapy, improvement was recorded in a 50% decrease in PASI. After 4 weeks of treatment, clinical remission was achieved in 70% of the patients, a significant improvement in 12% of the patients; the average value of PASI was 5.8 ± 0.9 (a 5.1-time decrease; $P < 0.01$).

In the 4th subgroup (2nd Group), there were 6 patients with psoriasis who underwent local treatment with Xemose Universal Emollient Cream in the complex therapy. This cream contains omega 3 and 6 PUFA, thermal water Uriage, etc. The patients were with a disease history from 1 year to 26 years. Xemose Universal Emollient Cream was used externally on rash of the left half of the body, and the symmetrical lesions of the right half of the body were treated with an indifferent lanolin-based cream. Treatment was started in the stationary stage (PASI index on average 13.0 ± 3.1). Five patients had over 10% of the skin affected, 1 patient had 5% of the skin affected. Treatment resulted in a significant decrease in the PASI index to 3.0 ± 0.6 (4.3 times). There was a significant reduction in itching (by 93%), infiltration of affected skin (by 83%), erythema (by 62%), and peeling (by 60%). According to the HAM test, the improvement of health indicators increased from 4.5 to 5.3 points, activity indicators changed from 5.1 to 5.6 points, and mood indicators changed from 5.6 to 5.7 points. Upon completion of the course of treatment, a good subjective tolerability of Xemose Emollient Universal Cream was established; it was easy to apply, had good absorbency, soft texture, quick moisturizing effect lasting for 12 hours; it gave no feeling of “oily film”, which was characteristic of an indifferent cream. In the areas of the skin on which Xemose Emollient Universal Cream was applied (left half of the body), the color of the rash elements was less bright; there was less infiltration and peeling, and the

skin was more elastic, less dry than on the right half of the body (where an indifferent cream was used).

Conclusion

For the first time, the mechanism of implementing an anti-inflammatory effect of the experimental medicines containing omega-3 and 6 polyunsaturated fatty acids (Omegaven, Vitamin F99 cream rich), – an antioxidant effect – when treating simple irritant contact dermatitis; that is the weakening of the severity of oxidative stress. (decompensation in the lipid peroxidation system). For the first time, the greatest contribution of an increased activity of catalase to the weakening of oxidative stress in the affected skin is shown. Histopathological analysis revealed that, when treating experimental simple irritant contact dermatitis with Omegaven injections into the abdominal cavity and externally with Vitamin F99 cream rich, the infiltrates were less pronounced and there was a different composition of the cellular reaction in the lesions with predominating lymphocytes and macrophages than in those treated with Radevit ointment, which were characterized by a delayed acute phase of inflammation. The expediency of using Omegaven parenterally and the means of local therapy with omega-3 and 6 PUFA to treat inflammatory skin diseases is substantiated. Omegaven drug was used in the experiment according to the new clinical indications in simple irritant contact dermatitis

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