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CORRECTION OF PATHOLOGICAL CHANGES IN SALIVARY GLANDS OF ANIMALS WITH PACLITAXEL-INDUCED NEUROPATHY

Background. Paclitaxel is a highly effective chemotherapeutic agent used to treat breast, ovarian, and other cancers. At the same time, paclitaxel causes peripheral neuropathy as a side effect in 45%—70% of patients. **Aim**. The aim of the study was to investigate the effect of paclitaxel-induced peripheral neuropathy on the development of pathological changes in the salivary glands of animals and to explore the possibility of correction of the identified changes with vitamin B/ATP complex. **Materials and Methods**. To simulate toxic neuropathy, animals were injected i/p with paclitaxel 2 mg/kg for 4 days. In order to correct the identified changes, rats were injected i/m with vitamin B/ATP complex (1 mg/kg) for 9 days. In the homogenate of the submandibular salivary glands, α-amylase activity, total proteolytic activity, total antitryptic activity, the content of medium mass molecules, thiobarbituric acid reactive substances (TBARS), oxidatively modified proteins, and catalase activity were determined. **Results**. A significant increase in the content of oxidatively modified proteins, medium mass molecules, and the content of TBARS and significant decrease in the activity of catalase and amylase were determined in the salivary glands of animals with toxic neuropathy compared to these parameters in intact animals. Administration of vitamin B/ATP complex for 9 days against the background of paclitaxel-induced neuropathy led to normalization of antitryptic activity and amylase activity, a significant decrease in the content of oxidatively modified proteins, medium mass molecules, and TBARS along with a significant increase in catalase activity in the salivary glands of animals compared to the untreated rats with neuropathy. **Conclusion**. Paclitaxel-induced neuropathy caused the development of pathological changes in the salivary glands of rats, which was evidenced by a carbonyl-oxidative stress and impaired protein synthetic function. The correction with vitamin B/ATP complex restored the protein-synthetic function and the proteinase-inhibitor balance, suppressed the oxidative stress and normalized free radical processes in the salivary glands of rats.

Keywords: paclitaxel, peripheral neuropathy, salivary glands, oxidative stress, vitamins, niacin, thiamine, cobalamin.

In 2020, 19.3 million new cases of cancer and almost 10.0 million cancer-related deaths were recorded worldwide. GLOBOCAN predicts that in 2040, the number of cancer cases in the world will reach 28.4 million [1, 2]. According to the updated data of the National Cancer Registry

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of Ukraine, in 2021, about 120,000 new cases of malignant neoplasms and 53,000 deaths were registered in Ukraine. At the end of 2021, more than 1 million people with oncological diseases were registered in medical institutions of Ukraine [3]. The annual mortality rate from oncological pathologies is almost 90 thousand patients, 35% of whom are people of working age [4].

Paclitaxel is a medication used to treat breast, ovarian, and other cancer types [5]. Despite its high effectiveness in blocking tumor progression, paclitaxel also causes peripheral neuropathy as a side effect in 45%—70% of patients [6, 7]. According to Seretny et al. (2014), paclitaxel-induced peripheral neuropathy affects from 44% to 98% of patients and can contribute to the disabling condition of pain from cancer chemotherapy [8].

The current clinical practice of lowering peripheral neuropathy induced by chemotherapy is to reduce or stop neurotoxicity [9]. However, the efficacy of paclitaxel may be impaired if the dose is reduced. No known therapy has been effective in preventing or treating peripheral neuropathy induced by chemotherapy. No single drug has been found to be effective in preventing or treating peripheral neuropathy induced by chemotherapy. In addition, all known treatment options are not universal, but a combination of therapies may be more effective than individual drugs in preventing peripheral neuropathy induced by chemotherapy [10, 11].

Proper functioning of the salivary glands is closely related to the activity of various body organs and systems, such as the adrenal glands, kidneys, thyroid and pancreas, genitals, digestive system and cardiovascular system. According to the studies, the decreased functional activity of salivary glands can lead to the impaired oral cleansing and, consequently, poor hygiene; decreased enamel resistance; impaired local immunity; observed negative effects on oral homeostasis, etc. [12].

Scientific studies suggest a potential association between diabetic neuropathy and certain oral complications, including oral burning syndrome, dry mouth, impaired taste and smell, periodontitis, tooth loss, temporomandibular joint dysfunction, etc.

Dry mouth was a common manifestation of both distal symmetrical polyneuropathy and autonomic neuropathy [13]. Xerostomia and hyposalivation were associated with neuropathy in 27.2% and 22.9% of cases, respectively [14]. It is generally accepted that the etiology of hyposalivation in diabetes is associated with impaired parasympathetic vasodilation due to diabetic autonomic neuropathy [15].

At the same time, the impact of chemotherapy-induced peripheral neuropathy on the oral organs remains poorly elucidated. In addition, there is no clear gold standard for the prevention and treatment of chemotherapy-induced peripheral neurotoxicity.

B vitamins have been found to play an important role in the prevention of chemotherapy-induced peripheral neuropathy, without affecting the efficacy of chemotherapy drugs, except high-dose vitamin B6 [11]. One of the consequences of vitamin B deficiency, especially B12 deficiency, is known to be neuropathies, usually accompanied by paresthesia, numbness, and ataxia. Vitamin B12 levels have been shown to decrease rapidly in some cancer patients, especially during chemotherapy, and clinical manifestations are noticeable after only a few months [16]. Animal studies by Hamity et al. (2017) showed that nicotinamide was both a protective and therapeutic option for tactile hypersensitivity (sensory neuropathy) and escape-avoidance behavior (motor behavior) that resulted from paclitaxel administration [17].

The aim of the study was to investigate the effect of paclitaxel-induced peripheral neuropathy on the development of pathological changes in the salivary glands of animals and to explore the possibility of correction of the identified changes with vitamin B/ATP complex.

Materials and Methods

The experimental studies were performed on 71 white outbred rats of both sexes weighing 180—220 g. During the experiments, the regulations of the 1997 Council of Europe Convention on Bioethics, the European Convention for the Protection of Vertebrate Animals used for experiments and other scientific purposes, and the general ethical principles of animal experiments adopted by the First National Congress of Ukraine on Bioethics were followed. To simulate toxic neuropathy, the animals were intraperitoneally injected with paclitaxel (Actavis Ltd; series 5GN5122) 2 mg/kg for 4

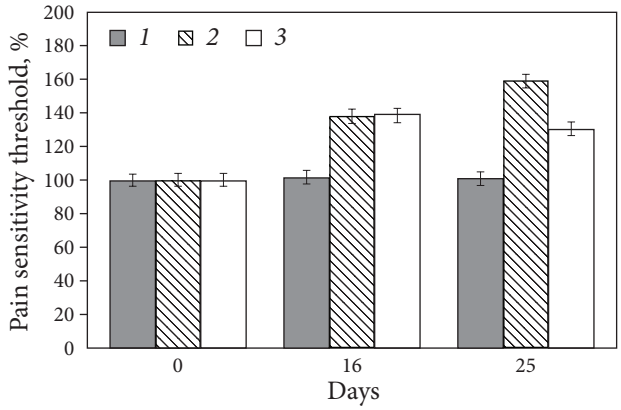
days (0, 2, 4, and 6). The development of paclitaxel-induced peripheral neuropathy was confirmed using the Randall — Selitto analgesimeter method [18]. In order to correct identified changes, rats were injected intramuscularly for 9 days with vitamin B/ATP complex commercially produced as Cocarnit (World Medicine) (1 mg/kg), which contains 50 mg cocarboxylase, 20 mg nicotinamide, 500 μg cyancobalamin, and 10 mg adenosine triphosphate dinatrium. Throughout the experiment, the animals were kept on a standard vivarium diet. The animals were removed from the experiment by bloodletting under thiopental anesthesia.

In the homogenate of the submandibular salivary glands of rats, the following biochemical assays were performed: α-amylase activity by Caraway, total proteolytic activity by Ugolev, total antitryptic activity by Veremeenko, the content of medium mass molecules by Gabrielyan, thiobarbituric acid reactive substances (TBARS) by Stalna, oxidatively modified proteins by Dubinina, and catalase activity by Korolyuk (the corresponding references to all these methods are given in [19]).

The results of the experimental studies were analyzed using methods of variation statistics. The test for deviation from the normal law was carried out by calculating the Shapiro — Wilk criterion. The reliability of the difference in the data, corresponding to the normal distribution, when comparing the arithmetic mean values was determined using Student's *t*-test for the independent samples. If the data series were not subjected to a normal distribution, the nonparametric Mann — Whitney test was used.

Results and Discussion

The administration of low doses of paclitaxel to rats for 4 days (0, 2, 4 and 6) induced mechanical hypersensitivity with a gradual onset. It took several weeks to reach the peak of paclitaxel-induced mechanical hypersensitivity, after which it remained elevated for several months, decreasing with time, and disappeared about 6 months after the first paclitaxel injection. Using the Randall — Selitto strain-gauge test, we found that control and experimental rats at the start of the paclitaxel-induced neuropathy simulation had a pain sensitivity threshold (PST) of 100%. The PST measurement



Pain sensitivity threshold (%) using the Randall — Selitto strain-gauge method in rats with toxic neuropathy and correction with vitamin B/ATP complex: *1* — intact rats; *2* — rats simulated with toxic neuropathy without correction; *3* — rats with toxic neuropathy injected with vitamin B/ATP complex for 9 days. * $p < 0.01$ compared to day 0 (before paclitaxel administration); # $p < 0.05$ compared to day 16

on the 16th and 25th day of the experiment showed its insignificant fluctuation within the baseline level. The increase in PST in rats with the toxic neuropathy modeling/simulating was significant on all days of the experiment compared to the initial value in the animals of the intact group: the PST increased by a factor of 1.3 on the 16th day of the experiment and by a factor of 1.6 on the 25th day of the experiment. There was also an increase in PST on the 25th day compared to the 16th day, indicating the development of toxic neuropathy (Figure).

According to the literature data, the neurotoxicity of paclitaxel has been experimentally proven by the direct damage to the peripheral nerves, the loss of the neuronal fibers, and demyelination caused by inhibition of tubulin depolymerization and consequently the impaired axonal transport of the major cellular components, causing the degeneration of the distal nerves [20]. Duggett et al. [21] suggested that most of the neurotoxic damage caused by paclitaxel is directed to the spinal cord ganglion and peripheral sensory nerves, which include the trigeminal nerve. Staff et al. [22] showed that paclitaxel induces an altered calcium signaling, the release of neuropeptides and growth factors, mitochondrial damage, and the formation of reactive oxygen species and can also activate ion channels that mediate responses to the extracellular signals. These various changes may be secon-

dary to the paclitaxel-induced effects on cytoskeletal microtubules. Pathophysiological processes induced by paclitaxel include inflammation, oxidative stress, and loss of mainly epidermal nerve fibers as well as changes in the mitochondrial function and excitability of peripheral neurons. In these models, paclitaxel treatment has been shown to affect different cell types in the peripheral and central nervous systems, including spinal cord ganglion neurons, Schwann cells, satellite glial cells, microglia, epidermis, and spinal astrocytes.

In the rats injected with vitamin B/ATP complex for 9 days after paclitaxel-induced neuropathy, PST on the 16th day was insignificantly different from PST in animals simulated with toxic neuropathy

Biochemical parameters of animal salivary glands in paclitaxel-induced peripheral neuropathy and correction with vitamin B/ATP complex

Biochemical parameters	Group 1 Intact	Group 2 Paclitaxel-induced neuropathy	Group 3 Paclitaxel-induced neuropathy + + vitamin B/ATP complex	Group 4 Intact + vitamin B/ ATP complex	*P*
Total proteolytic activity, μg/g·min	3.33 ± 0.06 (n = 9)	2.79 ± 0.19 (n = 25)	0.26 ± 0.07 (n = 22)	3.37 ± 0.13 (n = 8)	$P_{1-2} > 0.05$ $P_{1-3} > 0.05$ $P_{2-3} > 0.05$ $P_{1-4} > 0.05$ $P_{3-4} > 0.05$
Total antitryptic activity, g/kg	32.64 ± 1.74 (n = 9)	55.94 ± 6.53 (n = 20)	33.24 ± 2.38 (n = 22)	32.81 ± 1.96 (n = 8)	$P_{1-2} < 0.05$ $P_{1-3} > 0.05$ $P_{2-3} < 0.05$ $P_{1-4} > 0.05$ $P_{3-4} > 0.05$
Activity of α-amylase, mg/s·L	38.8 ± 4.67 (n = 10)	23.75 ± 1.61 (n = 25)	35.91 ± 3.71 (n = 22)	39.76 ± 2.93 (n = 7)	$P_{1-2} < 0.05$ $P_{1-3} > 0.05$ $P_{2-3} < 0.05$ $P_{1-4} > 0.05$ $P_{3-4} > 0.05$
Content of TBARS, μmol/g	4.25 ± 0.72 (n = 15)	9.62 ± 1.14 (n = 18)	6.69 ± 0.54 (n = 22)	4.27 ± 0.36 (n = 8)	$P_{1-2} < 0.001$ $P_{1-3} < 0.001$ $P_{2-3} < 0.05$ $P_{1-4} > 0.05$ $P_{3-4} < 0.01$
Content of medium mass molecules, n.u.	0.294 ± 0.003 (n = 8)	0.414 ± 0.019 (n = 25)	0.335 ± 0.014 (n = 22)	0.295 ± 0.006 (n = 8)	$P_{1-2} < 0.001$ $P_{1-3} > 0.05$ $P_{2-3} < 0.001$ $P_{1-4} > 0.05$ $P_{3-4} > 0.05$
Content of oxidatively modified proteins, n.u.	0.34 ± 0.02 (n = 10)	0.46 ± 0.03 (n = 26)	0.35 ± 0.03 (n = 20)	0.24 ± 0.03 (n = 8)	$P_{1-2} < 0.05$ $P_{1-3} > 0.05$ $P_{2-3} < 0.05$ $P_{1-4} < 0.05$ $P_{3-4} > 0.05$
Catalase activity, μkat/g·min	0.74 ± 0.034 (n = 10)	0.35 ± 0.047 (n = 18)	0.47 ± 0.035 (n = 20)	0.73 ± 0.014 (n = 8)	$P_{1-2} < 0.0001$ $P_{1-3} < 0.05$ $P_{2-3} < 0.05$ $P_{1-4} > 0.05$ $P_{3-4} < 0.05$

without correction and was less by a factor of 1.2 on the 25th day (Figure).

We established that the proteinase-inhibitory potential in the submandibular salivary glands of rats in paclitaxel-induced neuropathy did not change significantly compared to the control group (Table). Analyzing the total proteolytic activity of the salivary glands of animals in all studied groups, we found no statistically significant changes. The activity of proteinase inhibitors in animals with toxic neuropathy increased by 1.7 times compared to the control group (Table).

The administration of vitamin B/ATP complex for 9 days under the conditions of toxic neuropathy normalized the overall antitryptic activity of the submandibular salivary glands of rats compared to the group of animals that were simulated without neuropathy correction (Table).

Amylase activity in the salivary glands of paclitaxel-induced neuropathy in rats decreased by 1.6 times compared to control animals, indicating inhibition of protein-synthetic activity. The administration of vitamin B/ATP complex led to normalization of amylase activity in the submandibular salivary glands of the animals (Table).

Analyzing the development of carbonyl oxidative stress in the salivary glands of animals under modeling of toxic neuropathy, we found a significant increase in the content of oxidatively modified proteins by 1.4 times, in the content of medium mass molecules — by 1.4 times, and in the content of TBARS — by 2.3 times compared to these parameters in the intact animals (Table). The activity of catalase in the submandibular salivary glands of the animals under these conditions decreased twice as much as that of the control (Table). Thus, the development of paclitaxel-induced neuropathy is accompanied by the development of carbonyl oxidative stress in rat salivary glands. The findings are supported by numerous studies, in which paclitaxel has been shown to cause mitochondrial damage, leading to the formation of reactive oxygen species and the development of intra-axonal oxidative stress. For example, lipid peroxidation was found to increase and glutathione levels were elevated after treatment with paclitaxel, while the expression of the antioxidant enzyme, superoxide dismutase, was reduced in sciatic nerve neurons and the dorsal medullary ganglion [23, 24].

Administration of vitamin B/ATP complex for 9 days against the background of paclitaxel-induced neuropathy modeling led to a significant decrease in the content of oxidatively modified proteins, middle molecules, and TBARS in the salivary gland homogenate as compared to the rats with modeled toxic neuropathy. The activity of catalase in the salivary glands of rats injected with vitamin B/ATP complex for 9 days in paclitaxel-induced neuropathy increased significantly compared to the animals simulated without neuropathy correction, but lower compared to the intact animals (Table).

The attempts to prevent or treat toxic taxane-induced neuropathy are disappointing in clinical trials. The only clear success in a large randomized clinical trial was the demonstration that duloxetine provides moderate pain relief in patients with established chemo-induced peripheral neuropathy [25]. All other studies were either negative or showed benefits in small cohorts that were not reproduced [26]. Unsuccessful prophylaxis trials focused on diffuse neuroprotection and used agents that exert a cytoprotective antioxidant action and improve a mitochondrial function (amifostine, glutathione, vitamin E, and acetyl-L-carnitine). It is expected that more targeted prevention strategies that focus on the unique aspects of the pathogenesis of toxic neuropathy can prevent this complication, while preserving the tumor-killing properties of taxanes.

In our study, the administration of vitamin B/ATP complex for 9 days in rats with paclitaxel-induced neuropathy led to a significant decrease in the content of oxidatively modified proteins, medium mass molecules, and TBARS while catalase activity in the salivary glands' homogenate increased.

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КОРЕКЦІЯ ПАТОЛОГІЧНИХ ЗМІН У СЛИННИХ ЗАЛОЗАХ ТВАРИН ЗА УМОВ ПАКЛІТАКСЕЛ-ІНДУКОВАНОЇ НЕЙРОПАТІЇ

Паклітаксел — високоефективний хіміотерапевтичний засіб для лікування раку молочної залози, яєчників та ін. У той же час він спричиняє периферичну нейропатію як побічний ефект у 45—70% хворих. **Мета дослідження** — вивчити вплив паклітаксел-індукованої периферичної нейропатії на розвиток патологічних змін у слинних залозах тварин, а також з'ясувати можливість корекції виявлених змін комплексом вітамінів групи В та АТФ. **Матеріали і методи**. Нейропатію у тварин моделювали інтраперитонеальним введенням паклітакселу (2 мг/кг) упродовж 4 днів. Корекцію виявлених змін здійснювали введенням комплексу вітамінів групи В та АТФ протягом 9 діб. У гомогенаті піднижньощелепних слинних залоз визначали активність α-амілази, загальну протеолітичну активність, загальну антитриптичну активність, вміст молекул середньої маси, ТБК-активних продуктів, окисно-модифікованих білків та активність каталази. **Результати**. Встановлено, що за умов паклітаксел-індукованої нейропатії у піднижньощелепних слинних залозах щурів протеїназно-інгібіторний потенціал вірогідно не змінювався порівняно з контролем. Показано вірогідне збільшення вмісту окисно-модифікованих протеїнів, молекул середньої маси та вмісту ТБК-активних продуктів за умов моделювання токсичної нейропатії відносно контролю. Активність каталази та амілази у піднижньощелепних слинних залозах тварин при цьому вірогідно зменшувалась. Введення комплексу вітамінів групи В та АТФ впродовж 9 днів за умов токсичної невропатії нормалізувало загальну антитриптичну активність та активність амілази, приводило до вірогідного зниження вмісту окисно-модифікованих протеїнів, молекул середньої маси та вмісту ТБК-активних продуктів у гомогенаті слинних залоз тварин порівняно з групою щурів, яким моделювали токсичну нейропатію без корекції. Активність каталази в слинних залозах щурів, яким вводили комплекс вітамінів групи В та АТФ за умов паклітаксел-індукованої нейропатії, вірогідно збільшується у порівнянні з тваринами, яким моделювали невропатію без корекції, але є нижчою порівняно з інтактними тваринами. **Висновки**. Паклітаксел-індукована нейропатія викликає розвиток патологічних змін у слинних залозах щурів, про що свідчить карбонільно-оксидативний стрес та порушення білок-синтетичної функції. Експериментальна корекція комплексом вітамінів групи В та АТФ відновлювала білок-синтетичну функцію слинних залоз щурів, пригнічувала оксидативний стрес, нормалізувала вільнорадикальні процеси та відновлювала протеїназно-інгібіторний баланс.

Ключові слова: паклітаксел, периферична нейропатія, слинні залози, оксидативний стрес, вітаміни, ніацин, тіамін, кобаламін.