УДК 615.262.1:591.169.2:615.454.1:616.31
DOI 10.11603/1811-2471.2020.v.i3.11577

PHARMACOLOGICAL STUDIES OF THE DENTAL GEL OF COMBINED COMPOSITION

©O. O. Hrudnytska[1], Yu. S. Maslii[2], G. V. Zaychenko[1], O. A. Ruban[2]

[1]O. Bohomolets National Medical University, Kyiv
[2]National University of Pharmacy, Kharkiv

SUMMARY. The growing prevalence of periodontal and oral mucosa diseases results in increasing number of people in need of orthopedic treatment due to tooth loss, which, accordingly, requires quality dental care.

The aim – is to study the pharmacological action of a new dental drug of combined composition in the form of a mucoadhesive gel under the conditional name "Cholident" for the treatment and prevention of inflammatory diseases of the periodontium, oral mucosa and to facilitate adaptation to removable dentures.

Material and Methods. The study of antiexudative activity of the dental gel was performed on a model of carrageenan edema using electronic plethysmometer, manufactured by WPI. As a reference drug, "Kamistad®" gel (STADA Arzneimittel, AG, Germany) was used. Evaluation of the reparative effect of the gel was performed on the model of thermal burn. At light optical research of histologic micronutrients epithelialization, border zone creation, infiltration of inflammatory cells (macrophages) and angiogenesis have been evaluated.

Results. After application of the gel under study, the antiexudative effect began to appear after 30 minutes, as evidenced by a decrease in the volume of the affected paw, while a similar effect of the comparison drug was observed only 60 minutes after application to the paw. The study drug also showed a longer action, as the antiexudative effect was still observed 120 min after application, while in the control group there was no decrease in paw volume after 90 min of the experiment. Sustained decrease of the combustion wound area in the animals to which the studied gel was applied has been demonstrated. Activation of epithelial proliferation in the border area, increase in the height of regenerating epidermis and formation of a thin layer of cells in the combustion area, signs of demarcation zone formation, and increase in density of newly formed vessels in the border zone dermis have been revealed by the results of histological examination.

Conclusions. The results show that the studied gel has a moderate anti-inflammatory effect, which in severity and duration of action exceeds the comparison drug, reduces the local inflammatory response and promotes skin regeneration in the acute phase of combustion.

KEY WORDS: dental gel; antiexudative activity; reparative action.

Introduction. In recent decades, there has been a worldwide trend of steady growth of various dental pathologies, among which the leading place is occupied by diseases of the periodontium and oral mucosa, as well as lesions of similar etiologies that occur when using prostheses of different designs [1, 2].

According to the results of numerous epidemiological studies by both domestic and foreign authors, the largest and most common group of periodontal diseases is inflammatory ones – gingivitis, periodontitis and parodontosis, which account for 94–96 % of all periodontal diseases [3–7]. Thus, according to medical statistics, only 12 % of the population has a healthy periodontium, 53 % have initial inflammatory phenomena, 23 % have initial destructive changes, and 12 % have moderate and severe lesions. In persons older than 35 years, the proportion of initial periodontal changes progressively decreases by 26–15 % with a simultaneous increase in moderate and severe changes to 75 %, which are dominated by inflammatory-destructive changes of the periodontal complex with bleeding gums, pus, formation of periodontal pockets, loosening of teeth and their subsequent loss [8–10].

The most often used to treat periodontal pathologies are topical drugs. The most effective topical dosage form (DF), which allows implementing multifactorial and prolonged action on periodontal tissues and mucous membranes, is the gel form of a drug. The advantage of this DF is to provide a local therapeutic effect due to targeted, local application and retention of the drug on the surface of the mucous membrane, fixation due to bioadhesive properties, minimizing saliva leaching and prolonged contact of an API with tissues, creating a relatively high concentration of active pharmaceutical ingredients and their rapid penetration through the mucous membranes into the capillaries, which significantly increases the bioavailability of active substances [11–13].

The main requirement put forward to dental drugs for the treatment of the above diseases, is multimodal action – the presence of antimicrobial, anti-inflammatory, analgesic and regenerating effects [9, 14–17]. To this end, to the new pharmaceutical composition in the form of a gel it was decided to include a combination of APIs of natural and synthetic origin, namely: "Phytodent" tincture (PJSC "CPP Chervona zirka", Ukraine), choline salicylate 80 % (Basf Pharma, Switzerland) and lidocaine hydrochloride (Societa Italiana Medicinali Scandicci, Italy), which provide the necessary complex effect on the tissues of the oral cavity affected in periodontal disease, as well as in pa-

thologies or injuries of the mucous membrane caused by the use of dentures, which is very relevant today, given the prevalence of this procedure among patients of different ages [18, 19].

It is known that one of the disadvantages of any dental dosage form is the short duration of pharmacological effect. This is due to their contact with saliva, which dilutes medicinal products, reducing the residence time on mucous membranes. As mucoadhesive polymers approved for oral use, selected on the basis of microbiological, rheological, adhesive and osmotic studies, a combination of Carbomer Polacril 40P (Amedeo Brasca & C. Srl, Italy) with OraRez® W-100L16 (BOAI, China) was proposed to improve the bioavailability of the developed gel, providing it with good adhesion characteristics and, accordingly, prolonged action [20–22].

The aim of this work is to study the pharmacological action of a new dental drug of combined composition in the form of a mucoadhesive gel under the conditional name "Cholident" for the treatment and prevention of inflammatory diseases of the periodontium, oral mucosa and to facilitate adaptation to removable dentures.

Materials and Methods. The study of antiexudative (anti-inflammatory) activity of the dental gel was performed on male rats weighing 160–180 g in a model of carrageenan edema using an electronic plethysmometer, manufactured by WPI, Italy. The animal was fixed in the hands of the researcher, its limb was immersed in a plethysmometer tank with a fluid. The volume of the fluid extruded was used to determine the volume of the limb. Experimental animals were divided into two groups (study and control group) of 6 animals each. As a reference drug "Kamistad®" gel (STADA Arzneimittel, AG, Germany) was chosen, containing as API lidocaine hydrochloride and chamomile flower extract [23–25].

Carrageenan edema was simulated by subplantar administration of carrageenan solution (10 mg/mL) at a dose of 0.1 mL/100 grams of body weight (administration under the aponeurosis of the hind paw). The scheme of the experiment was as follows: to determine the initial volume of the paw, measure the volume of the paw 60 min after administration of the phlogogenic agent, apply the test gel to the inflamed paw and measure the volume of the inflamed paw 30, 60, 90 and 120 min after applying the gel. Calculated the percentage of change to the initial volume of the paw, as well as changes in the volume of the paw up to 1 h after the introduction of phlogogen [26].

The reparative activity of the gel was investigated on the model of thermal burn. The study was performed on male Wistar rats weighing 180–220 g. The day before the simulation of burns, the animal skin was depilated with a safe blade in the area of the lower third of the back. Animals under ketamine anesthesia (100 mg/kg) on the pre-shaved area of skin for 10 sec were applied two round metal plates heated to 100 °C, which corresponded to burns of III A–B – III–B degree according to clinical classification of burns and is characterized by lesions of the entire skin with complete death of hair follicles, sweat and sebaceous glands [27]. Such tissue damage has common mechanisms of development and to some extent corresponds to the manifestations of periodontitis. Treatment was performed from the first day after modeling the burn by applying a thin layer of gel once a day at the same time.

All animals used in the study of reparative activity of the test gel were divided into 6 groups:

- animals of group 1 were applied the gel for 1, 2, and 3rd day after the burn and on 4th day removed from the experiment;
- animals of group 2 were applied the gel on the 4th, 5th, 6th day after the burn and on the 7th day removed from the experiment;
- animals of group 3 were applied the gel on the 11th, 12th, 13th day after the burn and on the 14th day removed from the experiment;
- animals of group 4 were applied the gel on days 18, 19, and 20 after the burn and on day 21 removed from the experiment;
- group 5 – group of the comparison drug "Kamistad®";
- group 6 – group of control pathology (CP), animals from the first day after modeling the pathology were administered a neutral solution (isotonic sodium chloride solution) on the burn area and on days 4, 7, 14 and 21 were removed from the experiment.

Each study group consisted of 3 animals.

After removing the animals from the experiment, skin samples were taken for histological examination. The following morphological changes were evaluated in each group: the presence of inflammatory cells (macrophages) and neoangiogenesis, infiltration of inflammatory cells, epithelization, migration and proliferation of epitheliocytes, the formation of a boundary zone.

Evaluation of the reparative effect of test samples was also performed using the above model of skin burn wound. A semi-quantitative method was used in the light-optical examination of histological micronutrients. Evaluated the regeneration of skin tissues according to the scale [28]:

- regeneration of the epidermis (0 – no regeneration, 1 – mitosis and migration of individual epithelial cells, 2 – mitosis, migration of epitheliocytes, formation of a layer in the damaged area, 3 – complete regeneration);
- angiogenesis (0 – absent, 1 – weakly expressed (individual vessels), 2 – moderate (appearance of

separate foci of angiogenesis in the border zone), 3 – pronounced (new vessels in the border and damaged dermis);

● infiltration of inflammatory cells (0 – absent, 1 – weakly expressed, 2 – moderate, 3 – expressed).

Each criterion on the scale was evaluated for a single sample (case) and the mean values with standard deviations were calculated in comparison for groups of CP – animals with burns and animals after application of the gel "Cholident".

All manipulations and interventions, as well as euthanasia of animals were carried out in accordance with the "European Union Directive 2010/63/EU on the protection of animals used for scientific purposes" [29], as well as according to the "General Ethical Principles of Animal Experiments", adopted by the First National Congress of Bioethics (Kyiv, 2001) and the Law of Ukraine No. 3477-IV "On Protection of Animals from Cruelty" dated 21.02.2006.

Statistical processing of the obtained data was performed using Student's t-test [30].

Results. The anti-exudative effect of dental gel under the conditional name "Cholident" was studied in comparison with the gel "Kamistad®" – a drug with local anesthetic, antimicrobial and anti-inflammatory types of action for topical use in dentistry. The drugs were applied 1 h after administration of phlogogenic agent (PA), during the inflammatory reaction, characterized by the dominance of histamine and serotonin components of the inflammatory reaction. The results are shown in Table 1.

Table 1. Dynamics of antiexudative activity of test samples

Experimental group, n = 6	Stat. indicator	Initial values	60 min after the introduction of PA	Time after gel application			
				30 min	60 min	90 min	120 min
Cholident	M	0.82	1.07	0.97	0.96	1.12	1.11
	±m	0.034	0.044	0.022	0.021	0.031	0.042
	%[1]	-	-	-9.3	-10.2	+4.6	+3.7
	%[2]	-	+29.4*	+18.2	+16.1	+36.4	+35.6
Kamistad®	M	0.81	1.07	1.06	0.96	1.12	1.12
	±m	0.35	0.39	0.54	0.27	0.32	0.39
	%[1]	-	-	-0.93	-10.2	+5.6	+5.6
	%[2]	-	+32.01*	+30.9	+18.5	+47.9	+47.9

Notes: 1 – the percentage change in paw volume up to 1 hour of exudative reaction; 2 – the percentage change to the original volume of the paw; * p≤0.05.

The results in Table 1 show that in the experimental group 1 h after the introduction of carrageenan there was a moderate swelling, which consisted in increasing the volume of the paw by 29.4 %. A moderate anti-exudative effect, manifested as a decrease in the volume of the inflamed paw by 9.3–10.2 % was observed 0.5–1 h after application of Dental gel "Cholident" (1.5–2 h after administration of phlogogenic agent). In subsequent periods of time, the antiexudative effect was absent.

In the group of animals receiving the comparison drug, 1 h after administration of carrageenan, the volume of the paw increased by 32.1 %. "Kamistad®" gel showed a moderate anti-exudative effect only 2 h after administration of the phlogogenic agent (1 h after application of the drug on the paw). There was a decrease in paw volume by 10.2 % as compared to the pathology (1 h after administration of the phlogogenic agent). The volume of the paw exceeded its initial value by 18.5 %, which can be considered as a tendency to detect anti-inflammatory activity. In other periods of observation, the antiexudative effect was absent.

Thus, the claimed dental gel has shown a moderate antiexudative effect 1.5–2 h after administration of the phlogogenic agent. The probable mechanism of its action is associated with inhibition of the release of early inflammatory mediators such as kinins, histamine, but not prostaglandins. In terms of the severity of anti-inflammatory activity, the test samples showed a comparable effect, but the gel "Cholident" was superior to the comparison drug "Kamistad®" in the duration of the anti-exudative effect.

The ability of the drug to affect the regeneration process was tested on a model of a burn wound. The results are shown in Table 2.

Analysis of the results of histological examination (Table 2) has shown an increase in cellular infiltration in the dermis under the site of thermal burn and the border area from 4 to 21 days of the experiment. Signs of epidermis regeneration above the thermal damage in terms of 4 and 7 days were not detected, only some mitoses in the border zone, in the hair follicles were observed. On days 14 and 21, a regenerating epithelial wall was detected in the

Table 2. Semiquantitative assessment of skin regeneration according to histological examination, (M±m)

Experimental groups	Reepithelialization (mitosis in the border zone)	Mitosis in the hair follicles of the border zone	Angiogenesis in the border area	Infiltration of macrophages into the dermis of the burn area
CP, day 4	0.50±0.28	1.00±0.00	-	1.00±0.00
CP, day 7	0.75±0.25	0.50±0.28	0.75±0.25	2.75±0.25
CP, day 14	0.75±0.25	0.50±0.28	1.00±0.40	2.25±0.25
CP, day 21	1.50±0.28	1.00±0.00	1.00±0.00	2.75±0.25
CP + Cholident, day 4	0.75±0.25*	-	0.50±0.28	1.25±0.25
CP + Cholident, day 7	1.75±0.25*	1.50±0.28	0.50±0.28	2.00±0.00
CP + Cholident, day 14	1.50±0.28	1.50±0.28*	1.00±0.00	1.25±0.25
CP + Cholident, day 21	1.75±0.25*	1.00±0.00	1.25±0.25*	2.25±0.25

Note: * – deviations are significant in relation to animals of the CP group, p≤0.05.

border area of the skin as a result of mitotic activity of the epidermis basal layer cells, as well as signs of demarcation zone formation. Regeneration consisted in increasing the number of epithelial cells, increasing the height of the epidermis in the border area and the formation of a thin layer of cells in the burn area, under the destroyed epidermis, but in no case complete replacement of the burn-damaged area was achieved. An increase in the density of newly formed vessels in the dermis of the border zone and cellular infiltrate in all areas of the skin was recorded. Fibroblasts were diffusely distributed between collagen fibers.

After applying the gel, a tendency to reduce the infiltration of macrophages was detected, which is a morphological manifestation of a decrease in the local inflammatory reaction. Recovery was somewhat greater in the border zone, but it did not reach the level of reepithelization of the defect zone. An increase in mitosis in hair follicles was recorded on days 7 and 14. Mitosis and cell migration from follicles are evaluated as manifestations of the reparative reaction in the acute phase of burns and are a source of epidermis recovery [31]. Signs of angiogenesis, formation of separate blood vessels have been noted in the border zone.

Thus, the obtained results indicate that the studied gel "Cholident" reduces the local inflammatory reaction and tends to promote skin regeneration in the acute phase of burns.

Conclusions. 1. In the model of carrageenan edema of the foot in rats, the studied dental gel "Cholident" significantly reduced the local inflammatory response, showed a moderate anti-exudative effect, which was realized 1.5–2 hours after administration of the phlogogenic agent, and had a longer effect as compared to the reference drug "Kamistad®".

2. The study on burn wound model has confirmed the ability of gel "Cholident" to stimulate reparative processes and reduce the local inflammatory response, which was manifested by increase mitosis and intensification angiogenesis in the affected area.

3. Further in-depth studies using various types of model pathology are needed to comprehensively assess the therapeutic effect and elucidate the mechanisms of pharmacological action of the new dental gel of the combined composition "Cholident".

LIST OF LITERATURE

1. Benjamin R. M. Oral health: The silent epidemic / R. M. Benjamin // Public Health Rep. – 2010. – Vol. 125. – P. 158–159.

2. Oral diseases: a global public health challenge / M. A. Peres, L. M. D. Macpherson, R. J. Weyant [et al.] // Lancet. – 2019. – Vol. 394. – P. 249–260.

3. Bansal M. Assessment of the prevalence of periodontal diseases and treatment needs: A hospital-based study / M. Bansal, N. Mittal, T. Bali Singh // J. Indian Soc. Periodontol. – 2015. – Vol. 19 (2). – P. 211–215.

4. Nazir M. A. Prevalence of periodontal disease, its association with systemic diseases and prevention / M. A. Nazir // Int. J. Health Sci. – 2017. – Vol. 11 (2). – P. 72–80.

5. Baiju R. M. P. Prevalence and predictors of early periodontal disease among adolescents / R. M. P. Baiju, E. Peter, B. R. Nayar [et al.] // J. Indian Soc. Periodontol. – 2019. – Vol. 23 (4). – P. 356–361.

6. Determination of individual cephalometric characteristics of theocclusal plane in Ukrainian young men and young women with orthognatic bite / M. O. Dmitriev, I. V. Gunas, I. V. Dzevulska, I. V. Zhulkevych // Biomedical and Biosocial Anthropology. – 2018. – Vol. 4 (33). – P. 5–11.

7. (2020). Correspondence between dental and skeletal maturity parameters among patients with different sagittal relationships at the end of puberty period / M. Goncharuk-Khomyn, E. Akleyin, I. Zhulkevych [et al.] // J. Int. Dent. Med. Res. – Vol. 13 (1). – P. 223–228.

8. Малий Д. Ю. Епідеміологія захворювань пародонта: віковий аспект / Д. Ю. Малий, М. Ю. Антоненко // Клінічна медицина. – 2013. – № 4. – С. 41–43.

9. Шманько В. В. Сучасні підходи до лікування хвороб пародонта і слизової оболонки порожнини рота / В. В. Шманько, М. І. Котик, М. В. Микитів // Вісник наукових досліджень. – 2015. – № 4. – С. 71–74.

10. Інтегральна характеристика інфекційно-запальних захворювань порожнини рота / А. Л. Мельник, І. М. Довга, Г. Є. Христян [та ін.] // Клінічна та експериментальна патологія. – 2015. – Т. 14, № 1. – С. 215–220.

11. Mucoadhesive drug delivery system: an overview / B. M. Boddupalli, Z. N. K. Mohammed, R. A. Nath, D. Banji // J. Adv. Pharm. Technol. Res. – 2010. – Vol. 1. – P. 381–387.

12. Pragati S. Review: Recent advances in periodontal drug delivery systems / S. Pragati, S. Ashok, S. Kuldeep // Int. J. Drug Deliv. – 2009. – Vol. 1. – P. 14.

13. Kovalenko S. M. Methodological aspects of development of gels for treating inflammatory dental diseases / S. M. Kovalenko, N. V. Khokhlenkova, J. M. Azarenko // Asian J. Pharm. – 2017. – Vol. 11. – P. 129–135.

14. Dowd F. Pharmacology and therapeutics for dentistry / F. Dowd, B. Johnson, A. Mariotti. 7th Ed. – USA: Mosby, 2016. – 864 p.

15. Ali, H. Principles of drug therapy in dentistry. 1st Ed. – India: Jaypee Brothers Medical Publishers (P) Ltd., 2012. – 160 p.

16. Фармакологія : підручник для студ. стомат. ф-тів вищих навч. закладів / І. С. Чекман, В. М. Бобирьов, В. Й. Кресюн [та ін.]. – Вінниця : Нова Книга, 2014. – 432 с.

17. Фармакотерапія в стоматології : навч. посіб. / В. М. Бобирьов, Т. А. Петрова, Г. Ю. Островська, М. М. Рябушко. – Вінниця : Нова Книга, 2013. – 368 с.

18. Маслій Ю. С. Мікробіологічне обґрунтування вибору АФІ та їх концентрації у складі стоматологічного гелю / Ю. С. Маслій, О. А. Рубан, О. П. Стрілець // Український біофармацевтичний журнал. – 2017. – № 1 (48). – С. 58–63.

19. Justification of local anesthetic and choice of its concentration in composition of dental gel / Yu. S. Maslii, O. O. Hrudnytska, O. A. Ruban, G. V. Zaychenko // Фармацевтичний журнал. – 2019. – No. 3. – P. 49–55.

20. Ruban O. A. Research on the choice of rational concentration of the gel forming agent in the composition of dental gel / O. A. Ruban, Yu. S. Maslii // Annals of Mechnikov Institute. – 2019. – No. 2. – P. 29–33.

21. Choice of mucosal adhesive in the composition of a new dental gel / Yu. Maslii, O. Ruban, Yu. Levachkova [et al.] // Pharmakeftiki. – 2020. – Vol. 32, Issue 1. – P. 40–49.

22. Masliy Ju. S. The study of biopharmaceutical and adhesive characteristics of a dental gel / Ju. S. Masliy, O. A. Ruban // News of Pharmacy. – 2018. – Vol. 1. – P. 28–32.

23. Компендиум: лекарственные препараты. URL: http://compendium.com.ua.

24. Любомирский Г. Б. Применение препарата Камистад в процессе ортодонтического лечения зубочелюстных аномалий в подростковом периоде / Г. Б. Любомирский, Т. В. Любомирская, Э. Г. Любомирская // Стоматолог-практик. – 2013. – № 4. – С. 50–51.

25. Фаруазова С. Т. Применение Камистад геля в комплексной терапии заболеваний пародонта и слизистой полости рта / С. Т. Фаруазова // Медицина. – 2012. – № 6. – С. 9–11.

26. Стефанов О. В. Доклінічні дослідження лікарських засобів : методичні рекомендації/ За ред. О. В. Стефанова. – К.: Авіцена, 2001. – 528 с.

27. Експериментальне вивчення нових препаратів для місцевого лікування ран : метод. рек. / Л. В. Яковлєва, О. В. Ткачова, Я. О. Бутко, Ю. Б. Лар'яновська. – Х. : Вид-во НФаУ, 2013. – 52 с.

28. Булоян С. А. Действие мази дермафен на регенераторные процессы кожи белых крыс после экспериментального термического ожога / С. А. Булоян // Международный журнал прикладных и фундаментальных исследований. – 2015. – № 10 (ч. 2). – С. 268–272.

29. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes // Official J. Eur. Union. – 2010. – L276. – P. 33–79.

30. Лапач С. Н. Статистические методы в медикобиологических исследованиях с использованием Excel / С. Н. Лапач, А. В. Чубенко, П. Н. Бабич. – К. : МОРИОН, 2001. – 408 с.

31. Звягинцева Т. В. Морфологические изменения кожи крыс после термического ожога при применении мазевых препаратов с разным механизмом действия / Т. В. Звягинцева, А. В. Кривошапка, О. В. Наумова // Актуальні проблеми сучасної медицини. – 2011. – Т. 11, № 2 (34). – С. 34–38.

REFERENCES

1. Benjamin, R.M. (2010). Oral health: The silent epidemic. *Public Health Rep.,* 125, 158-159.

2. Peres, M.A., Macpherson, L.M.D., Weyant, R.J., Daly, B., Venturelli, R., Mathur, M.R., ..., & Watt, R.G. (2019). Oral diseases: a global public health challenge. *Lancet,* 394, 249-260.

3. Bansal, M., Mittal, N., & Singh, T.B. (2015). Assessment of the prevalence of periodontal diseases and treatment needs: A hospital-based study. *J. Indian Soc. Periodontol.,* 19 (2), 211-215.

4. Nazir, M.A. (2017). Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int. J. Health Sci.*, 11 (2). Retrieved from: https://www.ijhs.org.sa/index.php/journal/article/view/1406.

5. Baiju, R.M.P., Peter, E., Nayar, B.R., Varughese, J.M., & Varghese, N.O. (2019). Prevalence and predictors of early periodontal disease among adolescents. *J. Indian Soc. Periodontol.,* 23 (4), 356-361.

6. Dmitriev, M.O., Gunas, I.V., Dzevulska, I.V., & Zhulkevych, I.V. (2018). Determination of individual cephalometric characteristics of theocclusal plane in Ukrainian young men and young women withorthognatic bite. *Biomedical and Biosocial Anthropology,* 4 (33), 5-11.

7. Goncharuk-Khomyn, M., Akleyin, E., Zhulkevych, I., Nahirnyi, Y., Brekhlichuk, P., Mochalov, Y., ..., & Stoika, O. (2020). Correspondence between dental and skeletal maturity parameters among patients with different sagittal relationships at the end of puberty period. *J. Int. Dent. Med. Res.,* 13 (1), 223-228.

8. Malyy, D.Yu., & Antonenko, M.Yu. (2013). Epidemiolohiia zakhvoriuvan parodonta: vikovyi aspekt [Epidemio-

logy of periodontal disease: age aspect]. *Klinichna medytsyna – Clinical Medicine,* 4, 41-43 [in Ukrainian].

9. Shmanko, V.V., Kotyk, M.I., & Mykytiv, M.V. (2015). Suchasni pidkhody do likuvannia khvorob parodonta i slyzovoi obolonky porozhnyny rota [Current approaches to treatment of periodontal diseases and diseases of mucous membranes of the mouth]. *Visnyk naukovykh doslidzhen – Bulletin of Scientific Research,* 4, 71-74 [in Ukrainian].

10. Melnyk, A.L., Dovha, I.M., Khrystyan, H.Ye., Radchenko, O.O., Povolokina, I.V., & Kazmirchuk, V.V. (2015). Intehralna kharakterystyka infektsiino-zapalnykh zakhvoriuvan porozhnyny rota [Integral characteristics of infectious and inflammatory diseases of the oral cavity]. *Klinichna ta eksperymentalna patolohiia – Clinical and Experimental Pathology,* 14, 1, 215-220 [in Ukrainian].

11. Boddupalli, B.M., Mohammed, Z.N.K., Nath, R.A., & Banji, D. (2010). Mucoadhesive drug delivery system: an overview. *J. Adv. Pharm. Technol. Res.,* 1, 381-387.

12. Pragati, S., Ashok, S., & Kuldeep, S. (2009). Recent advances in periodontal drug delivery systems. *Int. J. Drug Deliv.,* 1, 14.

13. Kovalenko, S.M., Khokhlenkova, N.V., & Azarenko, J.M. (2017). Methodological aspects of development of gels for treating inflammatory dental diseases. *Asian J. Pharm.,* 11, 129-135.

14. Dowd, F., Johnson, B., & Mariotti A. (2016). *Pharmacology and therapeutics for dentistry.* 7th Ed. USA: Mosby.

15. Ali, H. (2012). *Principles of drug therapy in dentistry.* 1st Ed. India: Jaypee Brothers Medical Publishers (P) Ltd.

16. Chekman, I.S., Bobyrov, V.M., Kresyun, V.Y., Hodovan, V.V., Horchakova, N.O., Kazak, L.I., …, & Riabushko, M.M. (2014). *Farmakolohiia: pidruchnyk dlia stud. stomat. f-tiv vyshchykh navch. zakladiv [Pharmacology: a textbook for students. stomat. faculties of higher education. institutions].* Vinnytsia: Nova Knyha [in Ukrainian].

17. Bobyrov, V.M., Petrova, T.A., Ostrovska, H.Yu., & Riabushko, M.M. (2013). Farmakoterapiia v stomatolohii: navch. posib. [Pharmacotherapy in dentistry: textbook]. Vinnytsia: Nova Knyha [in Ukrainian].

18. Maslii, Yu.S., Ruban, O.A., & Strilets, O.P. (2017). Mikrobiolohichne obhruntuvannia vyboru AFI ta yikh kontsentratsii u skladi stomatolohichnoho heliu [Microbiological justification the choice of APIs and their concentration in composition of dental gel]. *Ukraïnskyi biofarmatsevtychnyi zhurnal – Ukrainian Biopharmaceutical Journal,* 1 (48), 58-63 [in Ukrainian].

19. Maslii, Yu.S., Hrudnytska, O.O., Ruban, O.A., & Zaychenko, G.V. (2019). Justification of local anesthetic and choice of its concentration in composition of dental gel. *Farmatsevtychnyi zhurnal – Pharmaceutical Journal,* 3, 49-55.

20. Ruban, O.A., & Maslii, Yu.S. (2019). Research on the choice of rational concentration of the gel forming agent in the composition of dental gel. *Annals of Mechnikov Institute,* 2, 29-33.

21. Maslii, Yu., Ruban, O., Levachkova, Yu., Gureyeva, S., & Kolisnyk, T. (2020). Choice of mucosal adhesive in the composition of a new dental gel. *Pharmakeftiki,* 32, 1, 40-49.

22. Masliy, Ju.S., & Ruban, O.A. (2018). The study of biopharmaceutical and adhesive characteristics of a dental gel. *News of Pharmacy,* 1, 28-32.

23. *Kompendium: lekarstvennyye preparaty [Compendium: Medicines].* Retrieved from: http://compendium.com.ua [in Russian].

24. Lyubomirskiy, G.B., Lyubomirskaya, T.V., & Lyubomirskaya, E.G. (2013). Primeneniye preparata Kamistad v protsesse ortodonticheskogo lecheniya zubochelyustnykh anomaliy v podrostkovom periode [Use of Kamistad in the process of orthodontic treatment of dentoalveolar anomalies in adolescence]. *Stomatolog-praktik – Dentist Practitioner,* 4, 50-51 [in Russian].

25. Faruazova, S.T. (2012). Primeneniye Kamistad gelya v kompleksnoy terapii zabolevaniy parodonta i slizistoy polosti rta [Application of Kamistad gel in the complex therapy of periodontal diseases and oral mucosa]. *Meditsina – Medicine,* 6, 9-11 [in Russian].

26. Stefanov, O.V. (Ed.). (2001). *Doklinichni doslidzhennia likarskykh zasobiv: metodychni rekomendatsii [Preclinical studies of drugs: guidelines].* Kyiv: Avitsena [in Ukrainian].

27. Yakovlyeva, L.V., Tkachova, O.V., Butko, Ya.O., & Laryanovska, Yu.B. (2013). *Eksperymentalne vyvchennia novykh preparativ dlia mistsevoho likuvannia ran: metod. rek. [Experimental study of new drugs for local treatment of wounds: guidelines].* Kharkiv: Vyd-vo NFaU [in Ukrainian].

28. Buloyan, S.A. (2015). Deystviye mazi dermafen na regeneratornyye protsessy kozhi belykh krys posle eksperimentalnogo termicheskogo ozhoga [The effect of dermaphen ointment on the regenerative processes of the skin of white rats after an experimental thermal burn]. *Mezhdunarodnyy zhurnal prikladnykh i fundamentalnykh issledovaniy – Int. J. Appl. Fundamental Res.,* 10 (part 2), 268-272 [in Russian].

29. (2010). Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. *Official J. Eur. Union,* L276, 33-79.

30. Lapach, S.N., Chubenko, A.V., & Babich, P.N. (2001). *Statisticheskiye metody v medikobiologicheskikh issledovaniyakh s ispolzovaniyem Excel [Statistical methods in biomedical research using Excel].* Kyiv: MORION [in Ukrainian].

31. Zvyagintseva, T.V., Krivoshapka, A.V., & Naumova, O.V. (2011). Morfologicheskiye izmeneniya kozhi krys posle termicheskogo ozhoga pri primenenii mazevykh preparatov s raznym mekhanizmom deystviya [Morphological changes in rat skin after thermal burns when using ointment preparations with different mechanisms of action]. *Aktualni problemy suchasnoi medytsyny – Actual Problems of Modern Medicine,* 11, 2 (34), 34-38 [in Ukrainian].

ФАРМАКОЛОГІЧНІ ДОСЛІДЖЕННЯ СТОМАТОЛОГІЧНОГО ГЕЛЮ КОМБІНОВАНОГО СКЛАДУ

©О. О. Грудницька[1], Ю. С. Маслій[2], Г. В. Зайченко[1], О. А. Рубан[2]

[1]Національний медичний університет імені О. О. Богомольця, Київ, Україна
[2]Національний фармацевтичний університет, Харків, Україна

РЕЗЮМЕ. Внаслідок зростання поширеності захворювань пародонта і слизової оболонки порожнини рота збільшується кількість людей, які потребують ортопедичного лікування внаслідок втрати зубів, що, відповідно, потребує якісної стоматологічної допомоги.

Мета – вивчення фармакологічної дії нового стоматологічного препарату комбінованого складу у формі мукоадгезивного гелю під умовною назвою «Холідент» для лікування та профілактики запальних захворювань пародонта, слизової оболонки порожнини рота та для полегшення адаптації до знімних протезів.

Матеріал і методи. Вивчення антиексудативної активності стоматологічного гелю проведено на моделі карагенінового набряку з використанням електронного плетизмометра (Plethysmometer, виробництва WPI, Італія). Як референтний препарат використано гель «Камістад®» (STADA Arzneimittel, AG, Німеччина). Оцінку репаративної дії гелю проводили на моделі термічного опіку. При світлооптичному дослідженні гістологічних мікропрепаратів оцінювали епітелізацію, створення пограничної зони, інфільтрацію запальних клітин (макрофагів) та ангіогенез.

Результати. Після нанесення досліджуваного гелю антиексудативний ефект починав проявлятися через 30 хв, про що свідчить зменшення об'єму ураженої лапи, в той час як аналогічний ефект препарату-порівняння спостерігався лише через 60 хв після аплікації на лапу. Також досліджуваний препарат виявив більш тривалу за часом дію, оскільки антиексудативний ефект продовжував спостерігатися через 120 хв після нанесення, тоді як у контрольній групі не відмічалося зменшення лапи за об'ємом після 90 хв експерименту. Аналіз вимірювання площі опікової рани у тварин, яким наносили досліджуваний гель, показав її стійке зменшення. Результати гістологічного дослідження встановили активацію проліферації епітелію у пограничній ділянці, збільшення висоти регенеруючого епідермісу і формування тонкого пласту клітин у ділянці опіку, ознаки формування демаркаційної зони, а також збільшення щільності новоутворених судин у дермі пограничної зони.

Висновки. Отриманими результатами встановлено, що досліджуваний гель чинить помірний протизапальний ефект, який за виразністю і тривалістю дії перевершує препарат порівняння, зменшує місцеву запальну реакцію та сприяє регенерації шкіри в гострій фазі опіку.

КЛЮЧОВІ СЛОВА: стоматологічний гель; антиексудативна активність; репаративна дія.

ФАРМАКОЛОГИЧЕСКИЕ ИССЛЕДОВАНИЯ СТОМАТОЛОГИЧЕСКОГО ГЕЛЯ С КОМБИНИРОВАННЫМ СОСТАВОМ

©Е. О. Грудницкая[1], Ю. С. Маслий[2], А. В. Зайченко[1], Е. А. Рубан[2]

[1]Национальный медицинский университет имени А. А. Богомольца, Киев, Украина
[2]Национальный фармацевтический университет, Харьков, Украина

РЕЗЮМЕ. В результате роста распространенности заболеваний пародонта и слизистой оболочки полости рта увеличивается число людей, нуждающихся в ортопедическом лечении в связи с потерей зубов и качественной стоматологической помощи.

Цель – изучение фармакологического действия нового стоматологического препарата комбинированного состава в виде мукоадгезивного геля под условным названием «Холидент» для лечения и профилактики воспалительных заболеваний пародонта, слизистой оболочки полости рта и для облегчения адаптации к съемным протезам.

Материал и методы. Исследование антиэкссудативной активности зубного геля проводилось на модели карагенинового отека с использованием электронного плетизмометра (производство WPI, Италия). В качестве эталонного препарата использовался гель «Камистад®» (STADA Arzneimittel, AG, Германия). Оценка репаративного действия геля проводилась на модели термических ожогов. При светооптическом анализе были оценены гистологические микропрепараты, определялись эпителизация, создание клеточного вала, инфильтрация воспалительных клеток (макрофагов) и ангиогенез.

Результаты. После применения исследованного геля антиэкссудативный эффект начал проявляться через 30 минут, о чем свидетельствует уменьшение объема пораженной лапы, в то время как аналогичный эффект препарата сравнения наблюдался только через 60 минут после нанесения на лапу. Также изученный препарат имел более длительный эффект, так как антиэкссудативное действие продолжало наблюдаться через 120 минут после нанесения, в то время как контрольная группа не показала снижения объема лапы через 90 минут от начала эксперимента. Анализ площади ожоговой раны у животных, которые получали лечение изучаемым гелем, показал ее устойчивое снижение. По результатам гистологического исследования установлены активизация распространения эпителия в пограничной зоне, увеличение высоты регенерирующего эпидермиса и образование тонкого слоя клеток в зоне ожога, признаки формирования демаркационной зоны, а также увеличение плотности вновь образованных сосудов в дерме пограничной зоны.

Выводы. Результаты показали, что изученный гель проявляет умеренный противовоспалительный эффект, который по выразительности и продолжительности действия превышает препарат сравнения, снижает местную воспалительную реакцию и способствует регенерации кожи в острой фазе ожога.

КЛЮЧЕВЫЕ СЛОВА: зубной гель; антиэкссудативная активность; репаративная активность.

Отримано 11.08.2020