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Increasing the natural resistance and survival of minks in case of unfavorable course of Aleutian disease

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Aleutian mink disease (AMD) caused by parvovirus is a real curse of the industrial mink breeding worldwide. Most minks infected with the AMD virus die, so the symptomatic treatment is aimed to extend the life of diseased minks until the fur maturation. This review contains an analysis of data obtained from the use of Gamavit (GM) and Phosprenyl (PP), which are widely used in practical veterinary medicine, including in fur animals, and have therapeutic efficacy for treating other parvovirus infections of carnivores.
Both drugs were administered to minks by mixing with feed at the rate of 0.1 ml per kg of body weight for GM and 0.05 ml per kg of body weight for PP.
In efficiency studies of the drugs on healthy animals, it was shown that they had a positive effect on the resistance of animals to adverse impacts (infections, feeding disorders, weaning). GM was most effective for increasing the fertility and number of kits per female, as well as for reducing the alimentary anemia, while PP was effective for increasing the survival rate of kits and contributed to their growth. Both drugs stimulated phagocytosis, increased SBA and SLA.
The combined use of PP and GM increased the survival rate of young animals by 7.3% and the number of kits per female by 0.45 animals, as well as increased the number of defect-free skins by 7%. In addition, it eliminated anemia and increased the level of hemoglobin and erythrocytes in minks affected with AMD, although they did not reach the lower limit of the norm. Moreover, the use of PP and GM increased the number of kits per female by 0.7 animals vs. control, while the mortality rate of young animals reduced by 9.8%.
Thus, the combined use of GM and PP in minks can increase the main natural resistance indicators (SBA, SLA levels, phagocytosis indicators, the absorption ability of peripheral blood granulocytes, the activity of natural killer cells) and significantly reduce anemia. Furthermore, the combined use of the drugs can increase the survival rate of young animals, the number of kits per female, reduce the live weight decrease in kits and increase the number of defect-free skins.
Keywords: *mink, Aleutian disease, parvoviruses, Phosprenyl, Gamavit, anemia.*

Повышение естественной резистентности и выживаемости норок при неблагополучии по алеутской болезни

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Алеутская болезнь норок (АБН), возбудителем которой служит парвовирус, является настоящим бичом для промышленного норководства во всем мире. Большинство инфицированных вирусом АБН норок погибают, поэтому цель симптоматического лечения состоит в том, чтобы продлить жизнь больным норкам до созревания волосяного покрова. В настоящем обзоре проанализированы данные об использовании при АБН Гамавита (ГМ) и Фоспренила (ФП) — препаратов, широко применяемых в практической ветеринарии, в том числе у пушных животных, и обладающих терапевтической эффективностью при других парвовирусных инфекциях плотоядных. Оба препарата давали норкам, размешивая их с кормом из расчета 0,1 мл/кг массы тела для ГМ, и 0,05 мл/кг массы тела для ФП.
При испытании эффективности препаратов на здоровом поголовье было показано, что они положительно влияют на устойчивость зверей к неблагоприятным воздействиям (инфекции, нарушения кормления, отсадка). ГМ был наиболее эффективен для повышения оплодотворяемости и выхода щенков, а также для уменьшения

белопухости, а ФП — для повышения сохранности и активизации роста щенков. Оба препарата стимулировали фагоцитоз, повышали БАСК и ЛАСК.
Сочетанное применение ФП и ГМ позволило повысить сохранность молодняка на 7,3 %, увеличить выход щенков на 0,45 щенка на самку и получить на 7 % больше шкурок без дефектов. Также у больных АБН норок удалось скорректировать анемию и повысить уровень гемоглобина и эритроцитов, хотя они не достигли нижней границы нормы. Кроме того, выход щенков от больных самок при использовании ФП и ГМ был на 0,7 щенка выше, чем в контроле, тогда как отход молодняка снизился на 9,8 %.
Таким образом, сочетанное применение ГМ и ФП норкам при АБН позволяет повысить основные показатели естественной резистентности организма (уровни БАСК, ЛАСК, показатели фагоцитоза, поглотительной способности гранулоцитов периферической крови, активности естественных киллерных клеток) и в значительной степени устранить анемию. Кроме того, сочетанное применение препаратов позволяет повысить сохранность молодняка, увеличить выход щенков на самку, уменьшить снижение живой массы щенков и получить больше шкурок без дефектов.
Ключевые слова: *норки, алеутская болезнь, парвовирусы, фоспренил, гамавит, анемия.*

Abbreviations (сокращения): AMD (АБН) — Aleutian mink disease (Алеутская болезнь норок), **GM (ГМ)** — Gamavit (Гамавит), **NK cells (ЕКК)** — natural killer cells (естественные киллерные клетки), **SLA (ЛАСК)** — serum lysozyme activity (лизоцимная активность сыворотки крови), **PP (ФП)** — Phosprenyl (Фоспренил), **SBA (БАСК)** — serum bactericidal activity (бактерицидная активность сыворотки крови).

Aleutian mink disease, or viral plasmacytosis, is literally a real curse of the industrial mink breeding worldwide [45]. The disease can become epizootic with the death of up to 90 % of diseased minks [43] and causes enormous economic damage manifested by a number of indicators: reduction of the total number of animals on the farm, decreased fertility of females, a mass death of mink kits, worsening of the fur quality, etc. [40, 42].

Causative agent, pathogenesis, clinical signs of AMD

The causative agent of AMD is a small DNA-containing parvovirus of the genus *Amdoparvovirus*, the family Parvoviridae [2]. The key virus reproduction protein is the NS1 nuclear protein, which possesses ATPase and helicase activity and contains sites through which its caspases — the main mediators of apoptosis — are recognized and cleaved [13]. In addition, there are two capsid proteins, VP1 and VP2, which are the main targets for the immune response [39]. There is no clear understanding of the mechanism how the AMD virus penetrates into cells [47].

The pathogenesis of AMD is similar in some respects to some mechanisms of the development of equine infectious anemia, hemolytic anemia, murine lymphocytic choriomeningitis and African swine fever, which are characterized by hypergammaglobulinemia. Two stages are distinguished in the pathogenesis of the disease: infectious and autoimmune.

The first stage proceeds in the same way as with most viral infections — it begins after the invasion and reproduction of the virus that stimulates proliferation of plasma cells that infiltrate many organs: lymph nodes, bone marrow, spleen, liver, kidneys, etc. [2]. Then, hypergammaglobulinemia develops with gamma globulins making up to 50 % of all serum proteins [38]. Interacting with the virus, antibodies form immune complexes, in which the virus preserves it infectious activity. Thus, antiviral antibodies exacerbate the development of AMD — a phenomenon of antibody-dependent enhancement of the infection can be observed. The inability of specific antibodies to neutralize the invading virus causes its lifelong persistence in the body. During the phagocytosis of immune complexes, macrophages release the virus, contributing to its subsequent multiplication in phagocytic cells. As a result, the immune response only contributes to the virus reactivation and impedes the recovery.

Moreover, the second stage with the AMD development is accompanied by an autoimmune process. The formed perivascular and glomerular complexes of the virus and antibodies are deposited on small blood vessel membranes, capillaries of renal vascular glomeruli, blood vessel walls of the liver and other organs, which leads to the development of necrotic arteritis, proliferative glomerulonephritis and other pathological conditions. It is supposed that it is the formation of such immune complexes that is the main reason for unsuccessful attempts of vaccination against AMD [37].

Clinical signs of AMD depend on the severity of the disease. Shortly before the death of the animals, they show aversion to food, depression, exhaustion, ulceration of the mucous membrane of the mouth, lips, gums, and renal failure. In addition, severe anemia develops due to the breakdown of red blood cells, decreased or inadequate erythropoiesis [44].

Most of the minks infected with the AMD virus die and those who had recovered from the disease fail to develop the immunity [40]. Formalin-inactivated vaccines against AMD contribute to only some increase in resistance of the animals. The main purpose of symptomatic treatment with vitamins, glucose, electrolyte solutions, immunomodulators, etc. is to prolong the life of sick minks before the fur maturation.

Use of immunomodulators and biostimulants

We have analyzed specific aspects of the use of immunomodulators and biostimulants in minks with AMD. In available published data, we found information on the use of drugs such as Levamisole, Thymogen, Polyoxidonium, Phosprenyl (PP) and Gamavit (GM) for this purpose.

It was shown that in minks spontaneously infected with the AMD virus, the number of red blood cells, the levels of hemoglobin and hematocrit are significantly lower than in healthy ones [33]. Levamisole had a weak and short-lasting immunomodulating effect on the body of minks with AMD, while the administration of polyoxidonium and thymogen contributed to a certain decrease in the intensity of pathological processes and autoimmune reactions, the infiltration of immune organs by plasma and mast cells [20].

However, most studies of AMD dealt with GM and PP — drugs that had long been used in practical veterinary medicine, including in fur animals [1, 3, 5, 8, 33]. GM is an effective immunomodulator [10], a metabolic and hematopoietic stimulator, which is successfully used for the treatment of clinically expressed infections, including those caused by parvoviruses [30], parasitic infestations [14, 28], various intoxications [12, 24] and other pathological conditions and stressful physiological periods of life. Its active ingredients are sodium nucleinate and denatured placenta extract. PP (the active substance is sodium polyprenyl phosphate) is an antiviral and immunomodulating agent that is effective in many viral infections of small domestic animals [23, 26]. It is also important that PP has proven clinical efficacy for the treatment of parvovirus infections in dogs (parvovirus enteritis) and cats (panleukopenia) [19, 26].

Both drugs were administered to minks by mixing with feed at the rate of 0.1 ml per kg of body weight for GM and 0.05 ml per kg of body weight for PP.

In efficiency studies of the drugs on healthy animals, experiments conducted on the Saltykovsky Animal Breeding Farm showed that both drugs had a positive effect on the resistance of animals to adverse impacts (infections, feeding disorders, weaning). GM was most effective for increasing the fertility and number of kits per female, as well as for reducing the alimentary anemia, while PP was effective for increasing the survival rate of kits and contributed to their growth [8]. Both drugs stimulated phagocytosis, increased SBA and SLA [9]. The incidence of staphylococcal infection in newborn kits was also prevented [21].

In another study conducted at Rechnoye CJSC in the Omsk Region, PP was administered i.m. It was found that PP increased the erythrocyte count in the peripheral blood of minks infected with the AMD virus by 13% (P<0.05) and the group of sick animals treated with PP showed an increased absorption capacity of peripheral blood granulocytes and enhanced quantitative indices of the phagocytic index and phagocytic number [4]. In another study conducted by the same animal breeding farm, after administration of PP to minks infected with the AMD virus, the number of erythrocytes increased by 14.9% and the level of hemoglobin grew by 7.5% (P<0.001 and P<0.05, respectively) [35].

Based on the results, a scheme was developed for the combined use of these drugs in case of unfavorable course of AMD. The purpose of this experiment was to maintain the level of natural resistance of animals spontaneously infected with AMD, to prevent the expected decrease in the number of kits per female, their death and to reduce a live weight decrease. Like in previous experiments, both drugs were given together with food in the same doses.

1. Results of the combined use of PP and GM in minks suspected of developing AMD
Результаты сочетанного применения ФП и ГМ у норок с подозрением на АБН

Indicators		Control (122 females)	Experiment (141 females)
Kits per female, animals		4.13±0.1	4.58±0.1*
Number of kits in the experiment, animals		400	400
Survival rate of young animals until slaughter, %		91.5	98.8*
Live weight of kits, g	females, 50 animals	2250±17	2310±21
	males, 50 animals	3820±26	3840±30
Defect-free skins, %		72	79 *
* significant differences (P<0.05) vs. control			

As can be seen from Table 1, the use of PP and GM allowed to increase the survival rate of young animals by 7.3 % and the number of kits per female by 0.45 animals. In addition, in the experimental group, the live weight of kits increased and the number of defect-free skins was more by 7% [22].

The following series of experiments studied the effect of the combined use of GM and PP on indicators of the erythroid lineage of hematopoiesis and natural resistance. When comparing the above scheme of the combined use of GM and PP (scheme 1) with a modified scheme, in which PP was additionally given with feed for the second time, 3 days before blood collection (scheme 2), the following results were obtained (Table 2).

2. Results of hematological and immunological studies of blood of the minks suspected of developing AMD
Результаты гематологического и иммунологического исследования крови норок с подозрением на АБН

Group	Hemoglobin, g/l	Erythrocytes, million	SBA, %	SLA, μg/ml
Control	12.7±0.6	4.8±0.1	21.8±0.1	56.7±0.9
Experiment, scheme 1 (standard scheme of PP + GM)	13.9±0.6	5.4±0.2	38.6±0.3	96.7±2.1
Experiment, scheme 2 PP + GM (+PP 3 days before blood collection)	15.7±0.5*	6.9±0.1**	44.9±0.2**	158.3±1.2**
Physiological norm	18.1±1.2	8.7±1.4	-	-
* significant differences (P<0.05) vs. control, ** P<0.01				

As can be seen from the data obtained, the hemoglobin level and the number of erythrocytes in control minks were lower, which is typical for anemia in AMD. In the experimental groups, the level of hemoglobin and erythrocytes significantly increased, but did not reach the norm. However, scheme 2 proved to be more effective. Similarly, the combined use of PP and GM in minks suspected of AMD according to scheme 1 resulted in an increase in SBA by 1.8 times, SLA by 1.7 times, while according to scheme 2 — by 2.1 and 2.8 times, respectively [22].

In the next series of experiments conducted in the Saltykovsky Animal Breeding Farm, the efficiency of the combined use of PP and GM in infected females was assessed on 699 animals. They were included into an experimental group. In the control group, which included both seronegative minks (3781 animals) and minks suspected of AMD (2160 animals), 27 % were positively reacting females at the beginning of the experiment. Seronegative females that remained after isolation of positively reacting ones served as additional controls.

3. Effect of PP and GM on the number of kits per female and survival rate of young American minks of sapphire color diseased with AMD
Влияние ФП и ГМ на выход и сохранность молодняка американских норок окраса «сапфир», больных АБН

Indicator	Experiment 699 animals	Control	
		Suspected of AMD (2160 animals)	Negatively reacting (3781 animals)
Females affected with AMD, %	100	27	0
Kits per female, animals	4.9 ± 0.1	4.2±0.1	5.1±0.1
Mortality of young animals, %	3.2	13.0	5.8

The experiments showed (Table 3) that the use of PP and GM increased the number of kits from diseased females by 0.7 animals vs. control (4.9 and 4.2, respectively, P<0.001). Moreover, the number of kits per female in the experimental group did not significantly

differ from negatively reacting control animals (4.9 and 5.1, respectively; P>0.05). The mortality rate of young animals in the experimental group was lower by 9.8% vs. control — animals suspected of AMD (3.2 and 13%, respectively). **It should be emphasized that the mortality rate of young animals was even lower than for control negatively reacting, i.e. healthy, animals.**

Since there are no effective specific remedies for treating AMD, the main task of the combined symptomatic treatment regimens for this disease is to improve the condition of sick minks, to maintain the fur quality and to prolong the life of animals to the maximum extent until the fur maturation. We believe that GM and PP are most suitable for solving this problem. The use of these drugs can increase the main natural resistance indicators (SBA, SLA levels, phagocytosis indicators, the absorption ability of peripheral blood granulocytes, the activity of NK cells), significantly reduce anemia (increase the number of erythrocytes and the hemoglobin level almost to the lower limit of the norm). In addition, the combined use of GM and PP for treating AMD can increase the survival rate of young animals, the number of kits per female, reduce the live weight decrease in kits and increase the number of defect-free skins by 7 %.

As one of the features of the course of AMD is antibody-dependent enhancement of the disease, it is important to note that PP has proven therapeutic efficacy for treating flavivirus infections [16, 18], in the pathogenesis which, like in AMD, an antibody-dependent enhancement of a viral infection plays an important role [17]. In addition, hemolytic anemia, which increases with the progression of the disease, is of great importance in the pathogenesis of AMD. We cannot disregard the important role of GM in the reduction of anemia.

It has been repeatedly shown that GM eliminates anemia and restores the erythroid lineage of hematopoiesis in stressful conditions [6], congenital iron deficiency [7], blood parasitic diseases in dogs [*14*, 25, 27], cats [29], northern deer [15, 32] and other animals [26]. Moreover, GM effectively restored erythropoiesis in experimental hemolytic anemia caused by phenylhydrazine [31]. The mechanism of development of toxic anemia in the latter case is associated with a blockade in the binding of erythropoietin to receptors leading to disruption of the JAK-STAT signaling pathway and suppression of erythrocyte maturation [44]. GM has a positive effect on structures of the liver parenchyma in minks [36].

Thus, at present, GM and PP are apparently the only immunomodulatory (GM and PP) and antiviral (PP) therapeutic agents with obvious therapeutic efficacy for treating AMD. It is noticeable that both drugs have also proven themselves in the treatment of other mammalian parvovirus infections – feline panleukopenia [19] and canine parvovirus enteritis [26, 30].

Conflict of interests

The authors state that no conflict of interests exists.

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Юбилей: 65 лет М.П. Михайловой

Заслуженному ветеринарному врачу РФ, заместителю начальника ГБУ ЛО «СББЖ Ладейнопольского и Подпорожского районов» Марии Петровне Михайловой 07.10.2019 года исполнилось 65 лет.

После окончания средней школы, М.П. Михайлова поступила в Ленинградский ветеринарный институт. В 1979 г. успешно окончила его и была направлена в Одесскую область, где работала ветврачом на овцеводческом комплексе. В 1980 г. была принята на работу в качестве ветврача молочного комплекса на 1200 голов в Подпорожском районе Ленинградской области, где решала проблемы поддержания генофонда айрширской породы, внедряя практику искусственного осеменения коров.

В крупных комплексах с беспривязным содержанием животных, при их большом скоплении на ограниченных площадях нужно было тщательно проводить противоэпизоотические мероприятия по туберкулезу, бруцеллезу и лейкозу. В1997 г. Подпорожский район был оздоровлен от лейкоза. Была внедрена диспансеризация всего поголовья, что позволило своевременно выявлять больных коров и проводить лечебно-профилактические мероприятия. Существенно уменьшились заболеваемость по незаразным болезням, в том числе акушерско-гинекологической патологии, и яловость, снизилась заболеваемость по хирургическим болезням. В 90-е годы, когда не хватало квалифицированных животноводов, в Подпорожье при профтехучилище № 244 М.П. Михайлова открыла курс, где обучала будущих операторов машинного доения основам животноводства, физиологии животных и технологии доения коров.

За заслуги в области сельского хозяйства и многолетний, добросовестный труд Указом Президента Российской Федерации от 06.08.1997 года М.П. Михайловой присвоено звание «Заслуженный ветеринарный врач РФ».

Коллектив станции и друзья Марии Петровны сердечно поздравляют ее с юбилеем, желают крепкого здоровья, счастья в личной жизни и новых творческих успехов.

А.Я. Батраков, В.Н. Виденин, Е.Е. Макеева