World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(RESEARCH ARTICLE)

Check for updates

Some aspects of clinical trial of the drug "Vetmicoderm"

Ogloblina M. V [1], Bushueva I. V [2,*], Martynyshyn V. P [3], Hunchak V. M [3] and Parchenko V. V [2]

[1] *Petro Mohyla Black Sea National University, Ukraine.*
[2] *Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.*
[3] *Stepan Gzhytskyi National University of Veterinary Medicine and Biotechnologie, Ukraine.*

World Journal of Biology Pharmacy and Health Sciences, 2024, 18(02), 001–004

Publication history: Received on 04 December 2023; revised on 19 January 2024; accepted on 22 January 2024

Article DOI: https://doi.org/10.30574/wjbphs.2024.18.2.0017

Abstract

Our aim was to conduct some clinical trials of the drug «Vetmikoderm» and compare its effectiveness with the well-known agent «Triosan». Clinical trials to determine the therapeutic effectiveness of the drug «Vetmikoderm» were carried out at the veterinary clinic «BEST» (Zaporizhzhia) on two groups of dogs, formed by gradual recruitment (based on the owners' referral to the clinic). To determine the etiological factors contributing to the development of dermatosis, we conducted a study of skin microflora. The sensitivity of microorganisms and fungi to the action of the «Vetmikoderm» preparation was determined by the disc-diffusion method. In the process of diagnostic research, including microbiological studies, it was established that conditionally pathogenic microflora from affected areas of dogs' skin was represented by both microorganisms and fungi. At the same time, fungi prevailed in the microbiocenosis of the selected skin samples. It is worth noting that «Vetmikoderm» has a better fungicidal effect, while «Triosan» is evidently more effective in treating dermatoses with predominantly microbial contamination. It has been proven that the combined use of both drugs has a better influence on the recovery process in animals.

Keywords: 1,2,4-triazoles; Skin diseases of fungal etiology; Sensitivity of microorganisms; Fungi; Clinical studies; Vetmikoderm; Triosan

1. Introduction

Modern achievements in the chemistry of heterocyclic compounds convincingly prove the priority and prospectivity of searching for new biologically active substances among derivatives of 1,2,4-triazole [1, 2]. 1,2,4-thiazole and its substituted derivatives rightfully occupy leading positions among the diversity of new synthetic molecules [3, 4]. Possessing a wide spectrum of biological properties, 1,2,4-triazoles are low-toxic substances [5].

Among various dermatological diseases of domestic animals, dermatomycosis is the most widespread. Dermatomycoses include various fungal diseases (ringworm, trichophytosis, microsporia, favus) characterized by the appearance of limited lesions on the skin with broken and fragmented hair or the development of local or multiple (diffuse) inflammatory processes of the skin and its derivatives with the presence of exudate of various characters [6]. Effective therapy for this process involves the use of a complex of means and should be aimed at eliminating all factors contributing to the development of dermatosis. It should provide desensitization and activation of trophics of the affected skin area in combination with local drugs [6]. The treatment process mainly focuses on the comprehensive use of topical fungicidal and fungistatic agents, as systemic drugs have many contraindications. Soft dosage forms with antifungal action, when applied locally, directly affect the focus of infection or the already developed inflammatory process, the causative agents of the diseases, et cetera.

* Corresponding author: Bushueva I. V

As of today, some of the popular and widely used medicinal products for the treatment of skin diseases of fungal etiology are soft dosage forms, namely «Mikogel», «Ketoconazole», and «Vetmikoderm».

«Mikogel» inhibits the biosynthesis of ergosterol and changes the lipid composition of the membrane, causing the death of the fungal cell. It exhibits pronounced antifungal activity against dermatophytes (Microsporum canis, Trichophyton rubrum, Epidermophyton floccosum), fungi of the Candida, Cryptococcus genera, and some others, as well as fungi of the Aspergillus genus.

However, «Mikogel» has several contraindications: hypersensitivity to miconazole nitrate and/or other components of the medicinal product, skin diseases caused by herpes viruses. Also, caution should be exercised when using «Mikogel» in case of microcirculation disorders [7].

«Ketoconazole» is a synthetic derivative of imidazolidinedione, which exhibits antifungal activity against dermatophytes Trichophyton spp., Epidermophyton floccosum, and Microsporum spp., as well as yeasts, including Malassezia spp. and Candida spp. It has a particularly pronounced effect on Malassezia spp. Ketoconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the fungal membrane [7].

«Ketoconazole» also has some drawbacks—it may cause irritation, and cetostearyl alcohol, which is part of «Ketoconazole» can cause local skin reactions (such as contact dermatitis). It has a short and insufficient effectiveness, narrow focus—only proteolytic action, and prolonged use may lead to allergic reactions.

«Vetmikoderm» is a modern non-steroidal agent, the active substance of which belongs to the derivatives of 1,2,4-triazole. The antifungal action of 1,2,4-triazole derivatives is due to the disruption of the integrity of the fungal cell membrane; 1,2,4-triazoles interfere with the synthesis of ergosterol—the main structural component of the fungal cell membrane. The effect is associated with the inhibition of cytochrome P450-dependent enzymes, including 14α-demethylase (sterol 14-demethylase), which catalyze the reaction of converting lanosterol to ergosterol, leading to a disruption in the synthesis of ergosterol in the fungal cell membrane.

The bacteriostatic activity of 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)morpholine lies in disrupting the normal course of biochemical processes in microorganisms by inhibiting the activity of certain enzyme systems. This creates unfavorable conditions for the development and multiplication of microorganisms. The bactericidal action of 4-((5-(decylthio)-4-methyl-4H-1,2,4-triazol-3-yl)methyl)morpholine causes irreversible changes in the cell protoplasm (protein denaturation) and thus leads to the rapid death of microorganisms [7, 9].

Therefore, the use of the drug «Vetmikoderm» is effective for the treatment of the mentioned dermatological pathology. It possesses desensitizing properties, acts as a wound healing, anti-inflammatory, and antipruritic agent. Additionally, it has antimicrobial action [6]. The active substance of the «Vetmikoderm» belongs to alkyl derivatives of 1,2,4-triazole and is patented in Ukraine [8]. The physicochemical properties of the liniment «Vetmikoderm» have been previously investigated and published [8].

2. Materials and methods

Clinical trials to determine the therapeutic effectiveness of the drug «Vetmikoderm» were carried out at the veterinary clinic «BEST» (Zaporizhzhia) on two groups of dogs, formed by gradual recruitment (based on the owners' referral to the clinic). The control group of animals (24 individuals) was clinically healthy, without visible signs of skin pathology, with dense and shiny fur. Dogs in the experimental group (24 individuals) exhibited characteristic and visually similar symptoms of skin lesions and its derivatives.

To determine the etiological factors contributing to the development of dermatosis, we conducted a study of skin microflora. For dogs in the control group, swabs were taken from the interdigital area, lower neck, abdomen, or forearm. The material for microbiological research from diseased animals consisted of swabs from the affected areas of the skin. The swabs were taken from the entire wound area using a sterile applicator «Voles» on a plastic stick with a tube and a protective cap with Amies medium. Sterile test tubes were used, and 9 ml of sterile isotonic sodium chloride solution were added to each tube. Plastic sticks were placed in test tubes with a saline solution and placed on an electric vibrator for 10 minutes. After preparing all the dilutions, 0.1 ml of the solution was taken from each test tube with a sterile pipette and placed in Petri dishes with the appropriate selective medium. The solution was spread over the surface with a sterile spatula until it was completely absorbed into the agar. The «seeded» dishes were left on the table in the box for 15 minutes, after which they were incubated in a thermostat at a temperature of 37°C (MPA medium) and 38°C – Saburo dextrose agar. Microorganisms were identified using the Bergey's Manual. In addition, microscopic examination was

carried out on biomaterial obtained with a sterile toothbrush by "combing" the affected hair, scales, flakes, etc. It was transferred to a glass slide, 1-2 drops of mineral oil were added, and it was heated for a few minutes. After applying a 50% aqueous glycerin solution, it was covered with a coverslip, and under a microscope (×100-400), it was examined for the presence of arthrospores in the material.

The sensitivity of microorganisms and fungi to the action of the «Vetmikoderm» preparation was determined by the disc-diffusion method. Sterile Himedia discs, standardized according to ISO 9001:2015, ISO 13485:2012, WHO GMP, were loaded with the respective amounts of the test samples. In the experiment, a nutrient agar for the active growth of fungi (Saburo medium with a pH not lower than 6.0) was prepared, onto which strains of microbial cultures identified from previous swabs from affected areas of the skin were applied as a "lawn." Cups with pure cultures were dried, and then discs with the test agents were applied. After 70-72 hours of incubation in a thermostat (28°C), measurements of growth inhibition around the discs with antifungal substances were taken, and a conclusion was made regarding the sensitivity of dermatophytes to the action of the investigated preparation «Vetmikoderm» and «Triosan».

3. Results

As a result of the conducted microbiological studies (Table 1) to determine the sensitivity of the sown microflora on the special Sabouraud dextrose medium, it was found that the growth inhibition zone for the tested preparation «Vetmikoderm» was 12.0±3.0 mm, while for «Triosan» it was 8.0±3.0 mm.

Table 1 Sensitivity of microorganisms and fungi to «Vetmikoderm» and «Triosan» (Sabouraud medium), n= 12

Preparation	**Sample**											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Growth inhibition zone diameter, mm												
«Vetmikoderm»	12	7	6	11	11	13	10	15	11	12	12	15
«Triosan»	8	11	10	7	9	5	7	10	10	7	7	9

This is to notice that only in two out of 12 samples, the antifungal activity of the «Triosan» preparation was higher than the liniment «Vetmikoderm» we investigated. As for the sowing of isolated cultures from affected skin areas on meat-peptone agar, the picture regarding their sensitivity to both investigated medicinal products was somewhat different (Table 2).

Table 2 Sensitivity of microorganisms and fungi to «Vetmikoderm» and «Triosan» (MPA medium), n = 12

Preparation	**Sample**											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Growth inhibition zone diameter, mm												
«Vetmikoderm»	5	9	9	5	4	0	5	4	4	3	4	3
«Triosan»	8	6	5	10	9	8	9	7	9	9	7	6

4. Discussion

The analysis of the obtained results provides grounds to anticipate a better bactericidal and bacteriostatic effect of the «Triosan» preparation, as it ensured a larger zone of growth inhibition for microorganisms, especially on the nutrient medium MPA. For «Vetmikoderm» as in experiments on pure cultures of microorganisms and fungi, it was found that it exhibits a better fungicidal effect. Meanwhile, in terms of antimicrobial action, the formulated liniment somewhat lagged behind the «Triosan» preparation.

Therefore, in the process of diagnostic research, including microbiological studies, it was established that conditionally pathogenic microflora from affected areas of dogs' skin was represented by both microorganisms and fungi. At the same time, fungi prevailed in the microbiocenosis of the selected skin samples. Examining the effectiveness of the two preparations with a similar effect confirmed that they can be used to treat skin pathology caused by the association of

microorganisms and fungi. It is worth noting that «Vetmikoderm» has a better fungicidal effect, while «Triosan» is more effective for treating dermatoses with predominantly microbial contamination.

5. Conclusion

A study was conducted on the impact of the drugs «Vetmikoderm» and «Triosan» on the treatment process of dogs diagnosed with dermatomycosis. It is worth noting that «Vetmikoderm» has a better fungicidal effect, while «Triosan» is evidently more effective in treating dermatoses with predominantly microbial contamination. It has been proven that the combined use of both drugs has a better influence on the recovery process in animals.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

[1] O. A. Bihdan, V. V. Parchenko. Chemical modification and Physicochemical properties of new derivatives 5-(thiophen-3-ilmethyl)-4-R1-1,2,4-triazole-3-thiol. Research Journal of Pharmacy and Technology. 2021. 14(9):4621-9. doi:10.52711/0974-360X.2021.00803.

[2] Karpun, Y. O., Karpenko, Y. V., Parchenko, M. V., Bihdan, O.A. (2020). Molecular docking and bioavailability of S-alkyl derivatives 5-(3-fluorophenyl)-, 5-(5-bromofuran-2-yl)– and-(((3-(pyridin-4-yl)-1H-1,2,4-triazole-5-yl))thio)methyl)-4-methyl-4H-1,2,4-triazolein silico methods. Current issues in pharmacy and medicine: science and practice 2020; 13 (1): 38–45. https://doi.org/10.14739/2409-2932.2020.1.198122

[3] Hunchak, V. M., Martynyshyn, V. P., Gutyj, B. V., Hunchak, A. V., Stefanyshyn, O. M., & Parchenko, V. V. (2020). Impact of 1,2,4-thio-triazole derivative-based liniment on morphological and immunological blood parameters of dogs suffering from der-matomycoses. Regulatory Mechanisms in Biosystems, 11(2): 294–298. https://doi.org/10.15421/022044

[4] Zazharskyi V., Bigdan O., Parchenko V., Parchenko M., Fotina T., Davydenko P., Kulishenko O., Zazharskaya N., Borovik I. (2021). Antimicrobial Activity of Some Furans Containing 1,2,4- Triazoles. Archives of Pharmacy Practice, 12(2): 60-65. https://doi.org/10.51847/RbJb3waUBB

[5] Danilchenko D. M., Parchenko V. V. (2017). Antimicrobial activity of new 5-(furan-2-yl)-4-amino-1,2,4-triazole-3-thiol derivatives. Zaporozhye Medical Journal, 19(1): 105-107. https://doi.org/10.14739/2310-1210.2017.1.91735

[6] Hunchak, V. M., Martynyshyn, V. P., Gutyj, B. V., Hunchak, A. V., Stefanyshyn, O. M., & Parchenko, V. V. (2020). Impact of 1,2,4-thio-triazole derivative-based liniment on morphological and immunological blood parameters of dogs suffering from dermatomycoses. Regulatory Mechanisms in Biosystems, 11(2): 294-298. https://doi.org/10.15421/022044

[7] Ohloblina, M. V., Bushueva, I. V. (2022) Improvement of the pharmacotherapeutic properties of a drug for the treatment of skin diseases of fungal etiology by changing its composition (report 1). Scientific and technical progress and optimization of technological processes in the creation of medicinal products: materials of the IX scientific-practical conference with international participation (September 22-23, 2022). - Ternopil: TNMU:64-65.

[8] Parchenko, V. V.; Martynyshyn, V. P..; Hunchak, V. M. Method for obtaining 4-((5-decylthio-4H-1,2,4-triazole-3-yl)methyl)morpholine. Patent Ukraine 125007; publ. 24.02.2021, bul. No. 8.

[9] Martynyshyn V. P., Hunchak V. M., Yaroshenko A. I., Parchenko V. V., Shcherbyna R. O., Panacenko V. V., Hunchak A. V. (2019) Chromagraphic Research of Liniment which Active Substance Belongs To New Detivaties of 1,2,4-Triazole. Research Journal of Pharmaceutical, Biological and Chemical Sciences, RJPBCS. 10(1):806-811.