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Original Article

Efficacy of Novel Formulations of Ivermectin and Albendazole in Parasitic Infections of Sheep in the Altai Mountains of Russia

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Abstract

Background: Parasitic infections are widespread in sheep farms of the Russian Federation, including Siberia. The infection of sheep with helminths and parasitic arthropods with a range of 70% to 100% in different regions, contributes to a decrease in the productivity and quality of products, and even death of animals. This study aimed to formulate drugs with pronounced parasiticidal effects based on ivermectin and albendazole, widely used to treat animal entomoses and helminth infections.

Methods: New formulations in the form of solid dispersed compositions were prepared by mechanochemical modification of ivermectin and albendazole using arabinogalactan polysaccharide. The efficacy of preparations on gastrointestinal strongylosis and monieziosis, and melophagosis of sheep was determined by parasitological examination and analysis of feces and urine.

Results: The new formulations demonstrated increased solubility and parasiticidal activity due to the formation of inclusion complexes when interact with water. The maximum efficacy values (> 95% efficiency) against intestinal Strongylida and *Moniezia expansa,* and ectoparasitic *Melophagus ovinus* were seen in doses lower than the recommended doses of the starting drugs.

Conclusion: The increased parasiticidal activity of innovative compositions can be explained by increased water solubility and bioavailability of the preparations, due to formation of inclusion complexes. The results of this study suggests the possibility of a significant reduction in the dosages of composed substances without losing their parasiticidal activity.

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Introduction

Parasitic infestations are wide spread in sheep farms of the Russian Federation, including Siberia. The infection of sheep with helminths and ectoparasites with a range of 70% to 100% in various regions contributes to significant economic losses, due to decrease in the productivity and quality of the products, and death of animals (1-3). Among the main parasites of sheep in Gorny Altai are intestinal and pulmonary strongylid nematodes of genera *Ostertagia*, *Trichostrongylus*, *Nematodirus*, *Haemonchus*, *Protostrongylus, Dictiocaulus*, tape worms of genus *Moniezia* (*Moniezia benedeni* Blan., *M. expansa* Blan), lancet liver fluke *Dicrocelium dendriticum* Rudolphi, sheep botfly (*Oestrusovis L.*) and sheep ked (*Melophagusovinus L.*) (4-7). Parasitic arthropods in combination with helminths may cause disturbances in the host organism immune system and homeostasis, leading to diseases (8). Therefore, the prevention and treatment of mixed parasitic infestations is an urgent task of modern veterinary medicine. There is considerable amount of experience in animal husbandry on various anthelminthics and antiparasitic agents belonging to different classes of compounds that are effective against various parasites.

Different forms of albendazole (ALB) are widely used for the treatment of helminthiasis (9, 10). This drug is effective against different nematodes, cestodes and trematodes. The relatively high therapeutic doses needed for treatment of individual helminthioses (10–75 mg/kg BW) and the need for long courses of treatment are the main disadvantage of ALB (11). This drug reduces the infection of animals with fascioliasis, but is not active against young trematodes (12) and parasitic arthropods, largely explained by the low water solubility of the substance (11).

In the recent years, several antiparasitic preparations have been developed with a wide spectrum of action against many endo- and ectoparasites of animals. Among these drugs are anthelminthics containing ivermectin (IVM) as an active substance, which is a highly effective against nematodes and ectoparasites (13-16). However, IVM-based injectable preparations which contain solvents such as glyceroformal, propylene glycol and polyvinylpyrrolidone (PVP) have several disadvantages. Generally, these preparations have high viscosity at low ambient temperatures, which make them difficult to inject. In addition, these compounds may causes irritation and other immunologic reactions at the injection site. The precipitation of IVM in tissues may also have toxic effects on the animal body. Another drawback of IVM is its narrow spectrum of antiparasitic action, i.e. this drug is not effective on cestodes and trematodes of animals. Administration of ALB or IVM in combination with other antiparasitic drugs has shown to have greater antiparasitic effects (17, 18). Normally, these compositions have low bioavailability, as their active substances have low water solubility in their native forms (11). To increase the stabilizing effect of aqueous suspensions of anthelminthics, some additives are added to the compounds (19). The using of nanotechnology in pharmaceutical manufacturing creates a unique opportunity for designing new drug forms based on microcolloids, micelles, liposomes and microemulsions (20, 21). It has also become possible to create new forms of drugs that are easy to use and effective against endo- and ectoparasites of animals. However, these technologies require expensive materials and long preparation time, and create a large amount of waste material.

One of the methods for increasing the effectiveness of anthelminthic drugs is the mechanochemical modification of the substances with suitable water-soluble polymers (22-26). After mechanical treatment of hard forms of

drug substances and polymers, the solid dispersions (SD) are obtained in the form of fine free-flowing powders. These SDs form inclusion complexes (IC) with increased solubility in an aqueous medium, leading to higher efficacy of the compounds (27-29).

This study aimed to study the possibility of increasing water solubility of ALB and IVM by mechanochemical methods, as well as to study the efficacy of the obtained SD in different dosages against ovine intestinal helminthioses and melophagosis. To achieve this goal, the SD of ALB and IVM were prepared by their mechanochemical treatment with arabinogalactan (AG).

Materials and Methods

Chemicals

Sodium carboxymethyl cellulose (CMC, 99.6%) and ALB (99%) were obtained from Changzhou Jialing Medicine Industry Co. (Changzhou, China). Polysaccharide AG and IVM (97.5%) were obtained from Irkutsk Institute of Chemistry (Siberian branch, Russia) and Shandong Qilu King-Phar Pharmaceutical Co. (Jinan, China), respectively.

Preparation of SD

The process of mechanochemical joint treatment of IVM with AG was carried out by method (30). A similar method was applied to the joint machine for mixture of ALB and IVM with AG at the components weight ratio of 1/1/10.

Four antiparasitic compositions were prepared from the corresponding SD by adding CMC (Blanose™) in the following ratio of components (mass %): ALB (3.0), IVM (0.3), AG (16.5) and Blanose (0.25). The resultant Concentrate of SD of IVM and ALB (CSDIA) was a fine gray powder, placed in plastic bags and stored at 25–35 °C. Upon adding water, a stable, ready to use aqueous suspension was formed.

Ethical statement

The blinded, randomized, and placebo-controlled study was performed according to the Guidance for the Experimental Study of New Pharmacological Substances (31), the rules adopted by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (32), and the rules of Good Clinical Practice of the Russian Federation (33).

The trials were approved by the Council on Ethics at the Ministry of Health of Russia as Clinicaltrials.gov registration protocol №1–110; 14.01.2017.

Helminthioses and melophagosis of sheep

The experiments were carried out at a private farm (ChichinovaV.Yu." in Shebalinsky district of the Altai Republic) on 82 sheeps of Gorno-Altai breed with 6–8 month old and 25–35 kg weight, spontaneously infected with gastrointestinal strongyles and *Moniezia expansa*. During the experiment, the sheep did not graze on the pasture, and were kept indoor and fed according to the norms of feeding livestock (34). During experiments, the animals had access to water *ad libitum*. Three to four days prior to the experiments, corresponding fecal samples were studied using the McMaster counting method (35). The sheep were then randomly assigned to experimental groups with a similar degree of infection, to further determine the geometric mean number of eggs per gram (EPG) of feces (36). The same animals were used for infection with adult forms of sheep ked (*Melophagus ovinus L.*). All fleece of sheep was examined and the geometric mean number of parasites per animal was determined. Dead sheep ked were not taken into account.

Experiments

The naturally infected animals with intestinal helminths and sheep ked were randomly divided into five experimental groups of 10 and one control group of 20 animals.

Sheep of experimental groups 1–3 were orally administered with 5% aqueous suspensions of the preparations as following: 1.0; 2.0 and 3.0 mg/kg BW ALB, and 0.1 and 0.2 mg/kg BW IVM. Sheep of the groups 4 and 5 received separate preparations of non-mechanochemical treated IVM and ALB at dosage of 0.2 and 2.0 mg/kg BW, respectively. Three experimental and one control groups (3 animals each) were formed from the sheep infected with *Moniezia*. The experimental animals were orally administered with 5% aqueous suspensions of the CSDIA (IVM, 0.2 mg/kg BW and ALB, 1.0, 2.0, 3.0 mg/kg BW). All members of the control groups were orally received 0.5% Blanose suspension (0.6 ml/kg BW).

The efficacy of CSDIA against gastrointestinal strongyles and *Moniezia* of sheep was determined by the "control test" method based on the results of coproscopic examinations of animals, in which, the geometric mean value of the number of parasitic eggs in samples from the experimental and control groups was calculated before and 15 d after deworming of animals.

The efficacy of CSDIA against sheep ked was determined on the 15th day post drug administration by examining the fleece of sheep, and calculation of geometric mean values of the number of live parasites.

The experiments were carried out in accordance with the recommendations for evaluating the efficacy of anthelminthics in ruminants (cattle, sheep and goats) of the World Association for the Development of Veterinary Parasitology (36). The clinical parameters of temperature, heart rate, respiratory rate and scar movement, as well as behavior of sheep, were evaluated before and after the 1st, 3rd and 5th day of taking the medicine. Examinations were carried out daily in the morning prior to feeding, according to the methodology of veterinary clinical laboratory diagnostics (37).

Statistical Data Analysis

The parasiticidal activity of the preparations (Ef%) was calculated as a decrease in the geometric mean values of the number of parasites or helminthseggs of the experimental groups compared to the control. To compare the parasiticidal efficacy of CSDIA, a statistical analysis of data was carried out on the geometric mean of the number of helminths eggs or parasites. A parametric t-test was used to compare the differences between the experimental and control groups at a significance level of $P \leq 0.05$. The calculations were performed using the SAS statistical analysis software for Windows (ver. 8).

Results

The results of the water solubility analysis for the obtained SD are shown in Table 1. A significant increase in the solubility of ingredients in SD form was seen (>30 times for ALB and 10 times for IVM).

Table 1: Water solubility of SD based on ivermectin and albendazole

Compound	***Water solubility***	
	Absolute (mg/L)	Increased (times)
IVM (initial substance)	12.6	-
SD1 of composition IVM/AG (1/10)	147.9	12
ALB (initial substance)	1.0	-
SD2 of composition ALB/IVM/AG (1/1/10)	32.8	33

IVM=Ivermectin, ALB=Albendazole, AG=Arabinogalactan

Coproscopic examination of the control group showed that 95.0% of the animals were infected with gastrointestinal strongyles (2.805 EPG) and 25.0% with *Moniezia* (0.730 EPG). All animals of the control group were infected with imagoes of sheep ked, with an average geometric value of 1.041. Testing CSDIA against gastrointestinal strongyles, the mean values of EPG ranged from 0 to 0.622 in the experimental groups (Table 2).

Table 2: The efficiency of parasiticidal drugs against gastrointestinal *Strongylata*

Animal Group	*Drug*	*Dosage (mg/kg BW)*	*Number of sheep per group*	*EPG (geometric mean)*	*Efficacy[a] %*	*P-value[b]*
Control	Placebo	-	20	2.805	NA	NA
Treatment	CSDIA	IVM – 0.1 ALB – 1.0	10	0.622	77.8	< 0.01
Treatment	CSDIA	IVM – 0.2 ALB – 2.0	10	0.075	97.4	< 0.001
Treatment	CSDIA	IVM – 0.2 ALB – 3.0	10	0	100	NA
Treatment	IVM	0.2	10	0.649	76.9	< 0.01
Treatment	ALB	2.0	10	1.178	58.8	< 0.05

IVM = Ivermectin, ALB = Albendazole

[a] Percent of efficacy based on geometric means.

[b] Statistically significant at $P \leq 0.05$ when geometric means were compared to placebo

The efficacy of CSDIA in the treatment group administered with 0.1 mg/kg IVMand 1.0 mg/kg ALB was 77.8% ($P < 0.01$). In the group taken 0.2 mg/kg IVM and 2.0 mg/kg ALB, the efficacy was 97.4 % ($P<0.001$). The efficacy was 100% in the group administered with 0.2 mg/kg IVM and 3.0 mg/kg ALB. IVM at dose of 0.2 mg/kg showed an efficacy of 76.9% ($P<0.01$), and ALB at dose of 2.0 mg/kg presented an efficacy of 58.8% ($P<0.05$) against gastrointestinal strongyles with fecal EPG of 0.649 and 1.178, respectively. In general, the initial substances of IVM and ALB showed significantly lower parasiticidal activity. Due to the difficulties in isolation of *Moniezia* spp. parasites in feces, and irregular distribution of their indicators in samples (32), the effect of drugs on parasites could only be evaluated qualitatively. Table 3 presents statistical indicators of geometric mean values of the number of *Moniezia* spp. eggs in fecal samples of sheep after exposure to parasiticides. In the treatment groups, the mean values of EPG ranged from 0 to 0.549, when testing CSDIA against *Moniezia* spp. (Table 3).

Table 3: Statistical indicators of geometric mean values of the number of eggs when exposed to parasiticides against *Moniezia* spp. (32)

Animal Group	*Drug*	*Dosage (mg/kg BW)*	*Number of sheep per group*	*EPG (geometric mean)*	*P-value[a]*
Control	Placebo	-	20	0.730	NA
Treatment	CSDIA	IVM – 0.1 ALB – 1.0	10	0.549	< 0.05
Treatment	CSDIA	IVM– 0.2 ALB – 2.0	10	0	NA
Treatment	CSDIA	IVM – 0.2 ALB – 3.0	10	0	NA
Treatment	IVM substance	0.2	10	0.899	NA
Treatment	ALB substance	2.0	10	0.601	> 0.05

IVM = Ivermectin, ALB = Albendazole

[a] Statistically significant at $P \leq 0.05$ when geometric means were compared to placebo

The efficacy of CSDIA in the treatment group administered with IVM (0.1 mg/kg BW) + ALB (1.0 mg/kg BW) was 28.4% (P<0.05). The efficacy was 100%in groups with 0.2 mg/kg IVM + 2.0 mg/kg ALB and 0.2 mg/kg IVM + 3.0 mg/kg ALB.The IVM constituent (0.2 mg/kg BW) was turned out to be ineffective against *Moniezia* spp. with a mean EPG of 0.899. In addition, ALB (2.0 mg/kg BW) showed a low efficacy of 17.7% (P>0.05) at a mean EPGof 0.601 against *M. expansa* (Table 4).

Table 4: The efficiency of parasiticidal drugs against *Moniezia expansa* (postmortem examinations)

Animal Group	***Drug***	***Dosage (mg/kg BW)***	***Number of sheep per group***	***Number of helminths, units or pieces (geometric mean)***	***Efficacy[a] %***	***P-value [b]***
Control	Placebo	-	3	0.64	-	-
Treatment	CSDIA	IVM – 0.2 ALB – 1.0	3	0.2	68.8	< 0.05
Treatment	CSDIA	IVM – 0.2 ALB – 2.0	3	0.1	84.4	NA
Treatment	CSDIA	IVM – 0.2 ALB – 3.0	3	0	100	NA

[a] Percent efficacy based on geometric means.
[b] Statistically significant at P≤0.05 when geometric means were compared to placebo

Examining the intestines of 3 sheep of the control group in the CSDIA experiment showed that all animals were infected with *M. expansa* (Mean=0.64). The efficacy of CSDIA containing 1.0, 2.0 and 3.0 mg/kg BW ALB was 68.8%, 84.4% and 100%, respectively (Table 4).

Testing the CSDIA against *M. ovinus*in the experimental treatment groups (Table 5), the geometric mean number of sheep ked was found to be 0.160 for 0.1 mg/kg IVM + 1.0 mg/kg ALB, and 0.090 for 0.2 mg/kg IVM + 2.0 mg/kg ALB. The efficacy of CSDIA in the treatment group was 84.9% (P<0.01) with a dose of 0.1 mg/kg IVM + 1.0 mg/kg ALB, and 91.4% (P<0.001) with a dose of 0.2 mg/kg IVM + 2.0 mg/kg ALB.

Table 5: The efficiency of using of parasiticidal drugs against *Melophagus ovinus*

Animal Group	***Drug***	***Dosage (mg/kg BW)***	***Number of sheep in group***	***(Number of parasites (geometric mean)***	***Efficacy[a] %***	***P-value [b]***
	Placebo	-	20	1.041	NA	NA
Treatment	CSDIA	IVM – 0.1 ALB – 1.0	10	0.160	84.9	< 0.01
Treatment	CSDIA	IVM – 0.2 ALB – 2.0	10	0.090	91.4	< 0.001
Treatment	IVM	0.2	10	0.195	81.3	< 0.01
Treatment	ALB	2.0	10	0.941	9.6	> 0.05

[a] Percent efficacy based on geometric means.
[b] Statistically significant at P≤0.05 when geometric means were compared to placebo

The individual use of constituents against *M. ovinus* showed an efficacy of 81.3% ($P<0.01$) with 0.195 sheep ked for IVM at a dose of 0.2 mg/kg BW. However, ALB at a dose of 2.0 mg/kg BW was not effective (9.6%, $P>0.05$) with 0.941 sheep ked. The IVM substance showed a slightly lower activity against sheep ked, compared to mechanically modified CSDIA (91.4%). During clinical trials, no harmful effects of drugs and substances on animal health were detected. All biological parameters werematched withthe physiological norms characteristic of this animal species.

Discussion

A parasitic complex including mainly the nematodes of *Strongylata* suborder, tapeworms of *Moniezia* and *Dicrocelium* genera, sheep botfly (*Oestrus ovis L.*) and sheep ked (*Melophagus ovinus L.*) parasitize sheep in Siberia and Gorny Altai.

In doses recommended by the manufacturer, IVM has a high efficacy and wide parasiticidal spectrum against parasitic nematodes and arthropods, and ALB is effective against nematodes, cestodes, and with lesser activity against trematodes (9, 38, 39). Due to its poor solubility and low bioavailability, ALB is effective against sheep cestodes and trematodes at a rather high dose of 20-40 mg/kg (11). For veterinary practice however, it is important to control the number of main groups of pathogens simultaneously, therefore, using combinations of both substancesis necessary. In this regard, the SD of drugs are considered (40, 41) as suitable delivery systems for biologically active molecules, and are used to improve the biopharmaceutical characteristics of already known drugs. To increase the solubility, bioavailability and stability, and reduce toxic effects of drugs, SDs are the preferred forms for a number of commercial drugs of well-known pharmaceutical companies (41). There are several methods for obtaining SD of drugs, such as dissolving components with subsequent removal of solvents, melting of ingredients, co-precipitation, and joint grinding (42).

Our previous researches (23, 24), as well as the work of other researchers (19, 43) showed the possibility of improving the solubility and bioavailability of a number of poorly soluble medicinal substances, including ALB. These achievements has made a hope for success in complex preparations of IVM and ALB, the efficacy of previously well studied. Some researchers have reported the presence of a synergistic effect with the combined use of macrocyclic lactones and benzimidazoles, and a slowdown in the development of drug resistance in helminths to complex antiparasitic drugs (18, 44-46), therefore, the development of benzimidazoles was continued (47, 48). At the same time, the preparations obtained in the mechanochemical modification process with polymers has increased the activity against target helminths, with a decrease in the consumption rate of the initial substances. Moreover, the ALB constituent does not have an embryotropic effect (25). Based on previous investigations, improving the solubility of IVM and ALB would increase their bioavailability and efficacy as parasiticidal agents. This hypothesis was proven in the present study. The drug in the form of CSDIA showed much higher efficacy against gastrointestinal strongyloses and *M. expansa* at a dose much lower than the therapeutic dose of the initial substances. The complex CSDIA also greatly reduced the number of parasitic sheep ked (91.4%). The initial ALB at a dose of 2.0 mg/kg BW was not effective; the initial IVM also showed less activity. The CSDIA has shown high parasiticidal efficacy due to an increase the solubility of AS.

Conclusion

This study demonstrated the high efficacy of CSDIA against gastrointestinal strongyles, *M.*

expansa and *M. ovinus* in sheep at an oral dose of 0.2 mg/kg BW IVM and 2.0 mg/kg BW ALB.

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Conflict of interest

The authors declare that there is no conflict of interest.

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