Assessment of milk biosafety for the content of antiparasitic drugs used for human consumption in different countries: Review

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Abstract. Milk is a staple food consumed all over the world which has significant impact both economically and nutritionally. Even if the milk is nutritious and healthful, it can also contain antiparasitic drugs residues that dangerous to human health. Inappropriate using antiparasitic drugs for producing animals may cause serious disorder in humans. This review was aimed to find out and analyze how much the dosage of injections and the excretion period of antiparasitic drugs from animal milks have been studied for safe human consumption. Totally, 15 papers about antiparasitic drugs usage for different animals were analyzed. The results showed that the most studied animal to date is the cow for ivermectin, albendazole and abamectin residues. More research works are required to be done for animals as goats, sheep, and especially camels to know after how many periods of time antiparasitic drugs will be excreted. As camel milk gains popularity due to it is possessing therapeutic and immunostimulant properties, more experimental results are needed into veterinary drugs safety measures. One of the mainly used method to conduct experiment is high-performance liquid chromatography because of superior resolving power when separate mixtures.

1 Introduction

Antiparasitic medications are drugs that are used to treat or prevent diseases in animals. Commonly known as ectoparasiticides, endectocides, endoparasiticides which includes antiprotozoals and antihelmintics (*Figure 1.*). They are used to kill parasites as worms, nematodes, arthropods and others in animal organisms [1].

In case of endo types, vermicides and vermifuges are two ways that antihelmintic drugs attack parasitic worms. The worms are killed by vermicides, while worms are often expelled with the use of vermifuges in their live states. A medication that is more poisonous to the parasitic worm than the host would ideally have a broad therapeutic index, or anthelmintic effect. In addition to their chemical structure, anthelmintic medications can be categorized according to the class of parasitic worms they target. Albendazole is another broad-spectrum anthelmintic drug and is the first choice for the management of hydatid disease and cysticercosis, such as *Taenia saginata, Diphyllobothrium latum, and Taenia solium.*

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Ectoparasiticides are organisms that live externally on the skin of hosts. For instant, *Sarcoptes scabiei* is the trigger of scabies, a highly contagious pruritic disease. In order to treat scabies, ones can use lindane, permethrin, ivermectin, or benzyl benzoate. Over time, resistance to lindane and permethrin has grown. The best cure rates have been observed when permethrin is combined with oral ivermectin, topical ivermectin, and synergized pyrethrins [2].

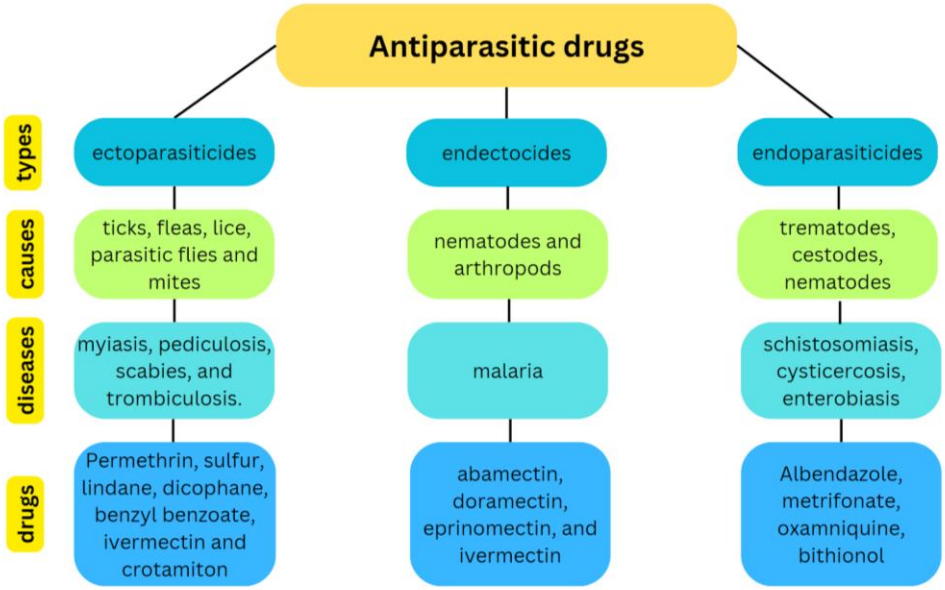

Fig.1. Classification of antiparasitic drugs

Drug residues have been recognized as one of the world's most important issues. Since 1962, one of the main areas of research has been the harmful consequences of medication leftovers. Experts from the Food and Agriculture Organization and World Health Organization came to the conclusion in 1983 that "foodborne disease was probably the most common health issue in the modern world" and "a major trigger to lower economic productivity". United Nations organized conference on environment and development in 1992 stated that food was a major means of transmitting chemical and biological environmental contaminants to human populations worldwide, and it urged governments all over to take action to reduce or eliminate these threats [3].

According the current study's aim, a literature knowledge about veterinary drugs residues in different countries and animals were collected and analyzed. Besides, this study consists information about mostly applied types of drugs with their dosage and well-liked technique from collected articles. In addition, significant research gaps and recommendations for future research are also presented.

2 Materials and methods

A systematic literature review was conducted in Google Scholar (https://scholar.google.com), PubMed (https://pubmed.ncbi.nlm.nih. gov), Science Direct (https://www.sciencedirect.com), and Web of Science (https://www.webofknowledge.com),

using the terms “antiparasitic drugs”, “residues in animal milks” and “antiparasitic drug residues”. In addition, references of selected articles were also studied for possible hits. Initially, a total of 15 papers were systematically analyzed and summarized according to the following parameters: (i) geographical location; (ii) number of articles; (iii) year of publication; (iv) sample type, which presented in the form of table. The data concerning the antiparasitic drug types which are mostly used for the treatment of infectious diseases in animals: ivermectin, albendazole, abamectin, oxfendazole.

3 Results and discussion

Regarding the geographical distribution of the studies which carried out shows that Spain stands out first with the number of 5 papers, followed by Argentina with 2 papers and after others countries (*Table 1*). However, other 8 countries presented only one publication. Also, majority of experiments are conducted in Spain because it is one of the milk producing countries.

Table 1. Information about country, number of articles, year, type of animal from collected papers

Country	Spain	Iran	Poland	China	Brazil	Argentina	Belgium	Egypt	Ethiopia	Turkey
Number of articles	5	1	1	1	1	2	1	1	1	1
Year	2013; 2015; 2016; 2021; 2023	2023	2015	2017	2019	2002; 2005	2000	2019	2019	2023
Type of animal	Goat; Sheep; Cow	Cow	Goat; Sheep	Cow	Goat; Sheep	Cow	Cow	Cow	Cow	Cow; Sheep; Goat
References	[4–8]	[9]	[10]	[11]	[12]	[13,14]	[15]	[16]	[17]	[18]

Information collected from papers of 2000 - 2023 years. Mostly, in the second half of the year, it found relatively more papers about milk detection to residues of antiparasitic substances. Peak years are 2019 and 2023. Over the years, publications in the area of milk production and safety are increasing. Summarizing the table shows that cow is the mainly used animal type for experiments with ivermectin, albendazole and abamectin residues. Because cow is an important model organism in the world, which provides almost all

nutritional foods and comparingly with others well studied. Nevertheless, for the same reason other types of animals should research more to avoid risk effects of veterinary drugs against humans. Data on camel milk was not found as noted in the table, because there was not enough research about dosage and usage of milk with antiparasitic drugs.

The types of antiparasitic drug consider in collected papers were allegedly used as drug residues that may ultimately be present in the milk, and the potential for a human health hazard posed by these drug residues.

In veterinary medicine, ivermectin is a common antiparasitic medication used to treat intestinal roundworm infestations. For cattle (c), sheep (s), horses (h): injectable (c, s), oral (c, s, h) and topical (c) products are available delivering ivermectin at 200 to 500 micrograms/kg [19]. After dosing 28 days must pass to consume milk to people in case of cow [20]. According to results of experiment conducted in Egypt, they used 60 samples of raw milk (cow) intended for human consumption and results showed that 18.3% (11/60) of the examined raw milk samples were contaminated with ivermectin residues [16]. It means that producers did not follow protocol rules to ensure a safe milk.

Albendazole, is a broad-spectrum anti-parasitic drug that treat lung and gastrointestinal nematodes, liver flukes, and tapeworms in animals. This drug is considered to work immediately against luminal parasites in the gastrointestinal tract, and their metabolites, which have already passed through the intestinal wall and liver, then become active against parasites inside organs and tissues. Albendazole has a broad dosage window and uses orally. The following is a list of some estimated albendazole dosages based on specific animal species: In horses, the dose for albendazole ranges from 5 mg/kg up to 25mg/kg; In sheep and goats, potential doses for albendazole may range from 5 mg/kg up to 15mg/kg depending on the infection; In cows, albendazole may be given at doses between 7.5mg/kg and 10mg/kg. Following results from experiment obtained in Argentina with cows, highest residual concentration (0.86 ± 0.33 μg ml^{-1}) at 12 h after oral administration of albendazole [13]. After 4-5 days milk treated with albendazole can be used for consumption of human [21].

Abamectin was tested for its anthelmintic activity against lungworm and two gastrointestinal worms. Widespread usage of the antiparasitic drug abamectin in animal husbandry is due to its demonstrated effectiveness against both endo- and ectoparasites of farm animals. Abamectin dosage must be 500 micrograms per kg bodyweight for cattle and after 35 days of slaughter for human consumption [22]. In experiment conducted with sheep, results showed maximal abamectin concentration (1277 ng/g) on day 3. A rapid loss of abamectin from sheep was seen during the first 32 days after which concentrations remained constant at approximately 77 ng/g and 300 ng/g, respectively [8].

The antiparasitic drug residues can be detected using ELISA, HPLC, UHPLC, Beta Star Combo and LC – MS. All of these techniques aimed to analyze components of milk to residue presence. The antiparasitic drug residue tests were conducted using mainly high-performance liquid chromatography (HPLC) analysis. It is no coincidence that HPLC is the most widely used analytical method. Capable of handling various types of analytes or samples, accurate and highly repeatable quantitative analysis, adaptable, automated functioning, and has high separation efficiency and sensitive detecting [23].

4 Conclusion

Overall, the revised data showed that determination of drug residues is a process which needs attention to avoid public health disease. The health threat is depending on dosage and after consumption period of time of antiparasitic drugs to animals. Veterinary drugs such as

ivermectin, albendazole, abamectin were discussed in case of residues excretion periods in animal milk. These drugs are recommended for use in many animal species like sheep, goat, cattle, horses and camel for control of both internal and external parasites. However, obtained experiments with these animals are not enough. Key findings of the study showed that ivermectin after dosing must pass 28 days to consume in case of cow milk. After 4-5 days cow milk treated with albendazole can be used for consumption. Cattle injected with abamectin after 35 days, sheep after 32 days could be used for human consumption. However, compared to other animal models, little is known about their dosage and periods of excretion from animals. The prolonged usage of these drugs in animals makes understanding of their significant. Milk of sheep, goat and camel should more tested for antiparasitic drugs residues in their milk due to lack of data. Future researches in this area could help prevent toxicity of antiparasitic drugs in human body which may cause serious consequences. Moreover, collecting research data may affect to specify exact protocols about each animals' quantity of dosage and period of excretion from their organism. Also, it could make life easier for companies and veterinarians that deal with dairy animals.

Conflict of interest

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization: D. Utemuratova and F.Amutova. Methodology: D. Utemuratova, Z.Kabdullina. Investigation: D. Utemuratova. Writing – Original Draft Preparation: D. Utemuratova. Writing – Review & Editing, D. Utemuratova. F.Amutova. Visualization: D. Utemuratova, F.Amutova, G. Konuspayeva. Supervision: F. Amutova. Project Administration: F.Amutova, G. Konuspayeva. Funding Acquisition: N. Akhmetsadykov.

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