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Research Paper

Anthelmintic resistance in cattle: A systematic review and meta-analysis

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ABSTRACT

A systematic review and meta-analysis was conducted to identify, evaluate, and synthesize primary literature reporting the efficacy of anthelmintic drugs in cattle. Information on the bibliographic data, anthelmintic drugs, animals, reduction method, days after application, parasite genera, type of application, and dosage were collected. The final data base was composed of 70 articles published between 1986 and 2016 with a total of 8,976 animals. The mode of application interfered with the efficacy of anthelmintic drugs in cattle ($P < 0.05$); oral application was superior to injectable and pour-on drugs. The combined use of drugs was superior to single macrocyclic lactones including ivermectin ($P < 0.05$), in this way the combined use was more effective than the single use of drugs for the control of gastro-intestinal nematodes in cattle ($P < 0.05$). Nematode genera in the abomasum (*Ostertagia* spp., *Haemonchus* spp.) and intestine (*Cooperia* spp.) were evaluated. Levamisole had a greater efficacy for *Cooperia* spp. than *Ostertagia* spp. ($P < 0.05$); ivermectin had a greater efficacy for *Ostertagia* spp. than *Haemonchus* spp. ($P < 0.05$); doramectin had a greater efficacy for *Ostertagia* spp. than *Cooperia* spp. ($P < 0.05$). Dosing in larger quantities and according to the manufacturer's recommendation was most efficient, and the dose limiting species differed between substance classes. The test based on the count of eggs per gram of faeces indicated a reduced efficacy of the drug as days passed following treatment. The forest plot did not show a difference ($P > 0.05$) between interventions (resistance and efficacy). The results of this systematic review and meta-analysis suggest that anthelmintic resistance in cattle is present on several continents. Therefore, there is a need to replace the schemes based on the exclusive use of drugs in order to decrease the selection pressure.

1. Introduction

Infections caused by gastro-intestinal nematodes (GIN) in the extensive system of livestock can cause serious economic problems (Demeler et al., 2009). This fact can be attributed to impaired animal health due to the presence of GIN, resulting in decreased production of meat and milk. To control these infections, anthelmintic drugs have been used for almost 40 years (Geurden et al., 2015). The classes of broad-spectrum anthelmintics range from benzimidazoles (BM), imidazothiazoles (IM)/tetrahydropyrimidens and macrocyclic lactones (ML), but salicylanilides, phenolic substitutes and organophosphates are also used (Molento et al., 2004). Broad-spectrum anthelmintics are more commonly used in ruminants because they are capable of eliminating large numbers of parasites, besides being of easy administration and safe to the hosts (Monteiro, 2011). However small-spectrum anthelmintics (salicylanilides, phenolic substitutes and organophosphates) have less use because they act in adults worms and partially in the immature stages of *Fasciola hepatica* (Oliveira-Sequeira and Amarante, 2001). Some also exert activity against hematophagous nematodes such as *Haemonchus* spp. (Taylor et al., 2010).

Anthelmintic resistance (AHR) in GIN can however arise (Stafford et al., 2010) due to risk factors associated to the use of anthelmintic, such as under-dosage (Maciel et al., 1996), overuse, and use of the same chemical compound without rotation. Sampling procedures for egg count per gram of feces (EPG) before and after application of a drug allow observing if AHR is present. If either percentage reduction in EPG is less than 95% or the 95% confidence level of EPG is less than 90%, AHR is suspected (Coles et al., 1992).

Occurrence of AHR against anthelmintics is an emerging problem in all parts of the world (Demeler et al., 2009), with some regions having particular large rates of AHR. In New Zealand, 90% of farms had AHR in 2005, but large AHR rates are also increasingly found in parts of Brazil, Argentina and Europe (Sutherland and Leathwick, 2011).

In recent years, several studies have been performed to investigate AHR in cattle. While all these studies may provide valuable isolated information, they sometimes describe conflicting results. One way to qualify and quantify such findings is through a systematic review (SR) and meta-analysis (MA) approach, which allows for the analysis and systematization of information. This type of approach combines the findings of several studies to make a reproducible summary of their

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Table 1
Population and outcome search term strings used for the final search in the systematic review of anthelmintic in cattle infected by gastrointestinal nematodes.

Acronym	Search string
Population	("cattle" OR "calves") ("beef" OR "dairy")
Outcome	(anthelmintic OR "macrocyclic lactone*" OR ivermectin OR moxidectin OR doramectin OR levamisole OR fenbendazole) AND (gastrointestinal OR internal) AND (parasite OR nematode OR worms OR worming) AND (resistance OR resistant) AND (efficacy OR effectiveness) AND (faecal egg count reduction test OR FECRT) AND (route of administration" OR "injectable formulation" OR oral OR pour on) AND ("natural infections")

data (Lovatto et al., 2007), providing the most substantive clinical evidence (Moher et al., 2010), based on defined methods that guide the search and inclusion criteria (Sargeant et al., 2006).

The aim of this SR-MA was to identify, evaluate, and synthesize primary literature reporting AHR of GIN in cattle. The rationale for this study was to generate information to help producers make evidence-based decisions and recommendations for a sustainable use of anthelmintic drugs.

2. Materials and methods

2.1. Systematization of information: Selection of articles

A systematic literature search was conducted in PubMed (Medline), Web of Science, and Google Scholar for publications made available through the State University of Ponta Grossa by the CAPES portal (*Periodicos da CAPES)*. All search terms are listed in Table 1. The information was extracted from the material and methods section and tables.

Studies were carefully evaluated according to their quality and relevance. At this stage, the information contained in each study was analyzed with regard to the experimental design, treatments and data analyzed. The main criterion for inclusion of the articles in the meta-analysis was the percentage of worms killed by the drug administered, to analyze the efficacy of anthelmintic drugs. Based on this criterion, the studies were selected by an evaluator, which was selected after training with an experienced professional. The results of the studies, i.e., either positive or negative effects of anthelmintics on GIN, were not used as selection criteria to create the database.

2.2. Tabulation and coding

Data were inserted into the Microsoft Excel (2010), where each line represented a treatment, and each column represented an exploratory parameter. The first variables were related to the bibliographic data (authors, year, periodical, country and home institution), followed by information about the animals (number of animals), the reduction methods (EPG counting or necropsy), days after application of anthelmintic drugs for EPG recount, mode of application (oral, injectable or pour-on), and dosage. Environmental characteristics and information about feed were not tabulated due to the information scarcity in most articles. Herds were not separated by the productive system, as the studies referred to beef and dairy cattle. Negative efficacy values were considered zero in the present study. The experimental characteristics are shown in Table 2.

Data from the database were evaluated based on either the entire dataset or portions of it. Efficacy of anthelmintics were analyzed for combination and unique drugs based on the entire dataset. For more specific analysis, the active principles were separated into ivermectin; doramectin; moxidectin (ML), levamisole (IM), fenbendazole (BM), or combinations: (i) eprinomectin and levamisole; (ii) moxidectin and levamisole; (iii) ivermectin and levamisole; (iv) doramectin and fenbendazole; (v) closantel and levamisole; (vi) moxidectin and albendazole; (vii) eprinomectin and fenbendazole; (viii) ivermectin and abamectin; (ix) doramectin and closantel; and (x) albendazole and closantel. The chemical groups of the respective active principle were tabulated to obtain a broader view of the effectiveness of the drugs most used around the world (i.e., ML, IM, BM and combinations).

2.3. Database description

The initial SR was composed of 150 publications of which 70 publications published between 1986 and 2006 were retained for further analysis, totaling 8,976 cattle. Publications were excluded if studies did not report the reduction percentage values of EPG, related to other animal species (sheep, goats, pigs), or used homeopathic products and artificial infections.

In the final database, 41% of the studies were executed in South America, 25% in North America, 14% in Oceania, 12% in Europe, 2% in Asia, 1% in Central America and Africa. With regard to the mode of application, injectable drugs were most often studied (51%), followed by a combination of modes of application (25%), pour-on (13%) and oral (9%) application. Initial and final EPG count was the most frequently used reduction method (85%), followed by count of larvae in the gastrointestinal system through necropsy (15%), and one study in which both procedures were applied.

The main GIN included in the final database were *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp., *Haemonchus* spp., *Oesophagostomum* spp., and multiple species. The dosage ranged for levamisole from 0.2 to 10.0 mg/kg, for moxidectin from 0.2 to 1.0 mg/kg, for ivermectin from 0.2 to 0.63 mg/kg, for doramectin from 0.2 to 0.7 mg/kg, for fenbendazole from 5 to 7.5 mg/kg and for combinations of drugs from 0.2 to 15.5 mg/kg of bodyweight.

2.4. Statistical analysis

A graphical analysis was used as a first step to evaluate the distribution, coherence and heterogeneity of the data (Lovatto et al., 2007). Through this analysis, hypotheses of relations were performed to define the statistical model. The definition of dependent and independent variables and the coding of data, that allows analysis of inter- and intra-experimental effects, were performed according to Lovatto et al. (2007) and Sauvant et al. (2008). Passive variables were submitted to analysis of variance and comparisons by Tukey test: i.e., the mode of application (oral, injectable or pour-on), chemical group, active principle, type of use (combination or unique), reduction method (EPG or necropsy). The GIN genera were analyzed separately for each active principle. The publication number was fixed in all analyses to exclude possible random effects. An analysis of prevalence of AHR for each anthelmintic family was made for continent by descriptive statistics. Prediction equations were developed from the coefficients obtained using the variance–covariance analysis. The equations were performed to evaluate the behavior of anthelmintic efficacy in relation to the days after application to recount of EPG and dosage. The analyses were performed using the program Minitab 17 (Minitab Inc., State College, USA).

A forest plot was made according to Neyeloff et al. (2012) in Microsoft Excel (2007) to analyze the efficacy of anthelmintic against GIN for each study based on the number of events and sample size. The forest plot represents all selected studies (n = 70) with confidence intervals of effect size at 95% illustrated by horizontal lines. The central line represents studies with no difference between interventions and separates the graph in studies with resistance (left side) and efficacy