

## Clinical Trials with Anthelmintics

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Clinical trials with anthelmintics are unique in that there are guidelines published how to do them in certain species. These guidelines may have to be observed to make studies acceptable by government regulations.<sup>(1)</sup>

Any discussion of clinical trials will have to recognize that clinical trials are just that: trials under clinical field conditions with products which have already been evaluated to some degree in other studies. Their efficacy and safety has already been established to some extent.

There are some common denominators for clinical trials with anthelmintics but also some variables that must be considered. Common denominators are:

The nature of the condition to be treated; worm parasitism.

The objective to collect information in a large population of the target species by several investigators under field conditions.

At least some results can usually be quantitatively and objectively measured (egg counts, larval counts, survival rate of the treated animals).

More and more, anthelmintics are used in seemingly healthy animals.

The variables are numerous and some are listed here:

a. Objectives of the Trial -

While all clinical trials with anthelmintics have the purpose in common to combat worm infestations, they may still differ in their objectives. A trial intended to support claims in an NADA may differ from one done with an approved product. Elimination of an existing worm infestation or prevention of new infections, demonstration of improved performance, practicality of use under field conditions, are some of the questions that may be addressed in clinical trials.

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The objective of an anthelmintic trial has to be realistic: animals that don't carry worms are not good subjects for a trial. It is difficult or impossible to keep parasitized animals untreated for an extended period of time. It cannot be assumed that an existing worm population remains the same over an extended period of time. Worm burdens may change with progressing age (ascarids, strongyloides), with dietary or management changes (cattle entering a feedlot). Therefore, the objective must be to determine worm removal under defined conditions, in some cases compared to untreated controls.

The limitations for field studies must be recognized. An involved study with repeated handling and sampling of animals is no longer a "field" study. The protocol for a true field study must resemble field conditions as much as possible. If an involved protocol is needed to serve given objectives, a well designed study under closely controlled conditions may be a better alternative. One may argue then if this is a clinical trial or a laboratory trial, but this argument should not affect the validity of the results. I prefer not to call an involved study with many extrinsic procedures a trial under field conditions.

Once the objectives and, therefore, the parameters to be measured have been determined, a study can be designed accordingly. If a study is designed to be demonstrating strictly an antiparasitic effect, a relatively simple design will do. If a study is meant to also show differences in the performance of the target animals with or without anthelmintic treatment, the appropriate parameters have to be measured. We believe that performance studies are not necessary to show that an anthelmintic is effective. But, they may be necessary to demonstrate the benefit of deworming to the owners of food producing animals or their veterinarians and other advisors. Such a study has to be designed as a performance study with balanced replicates over the period throughout which animals are expected to perform. The animals should be subjected as far as possible only to procedures common for the type of animal in the region where the study is performed. Everyone who has ever done such a study has learned how misleading intermediate measurements may be. In cattle, the measuring of grade, yield and carcass quality may allow more exact comparisons than live weights at closeout.

"Read the Label" is a slogan promoted by the manufacturers of animal health products and we all agree that this is essential for the proper use of any drug. Clinical trials offer an opportunity to make sure that the label instructions are complete, understandable and practical.

While clinical studies with anthelmintics must be well designed, it is also possible to "over design" a study. An example that comes to mind is the inclusion of placebo treatment. This should not be an absolute requirement. It may be impractical or impossible to include untreated controls: treated controls or delayed treatment of controls may be viable alternatives. The statistical analysis of results cannot be an absolute requirement. Some advocate the blind examination of fecal samples for worm eggs. I don't believe this is necessary in every case. I would prefer to weed out investigators who produce knowingly false data. The risk of failure in the market place is great if the initial evaluation is based on faulty studies.

b. The Target Animal -

Different study designs will be needed:

If the target animals are food producing animals or non-food producing animals,

If they are companion animals or animals kept for commercial purposes in the wider sense,

If they are wildlife animals,

If they belong to one or another species,

If they are treated individually or as a group.

The development of a new anthelmintic just as that of any new drug for animals provides for an expanding number of animals to be exposed to the drug, covering more and more varied conditions and types of animals. With that, the chances increase that previously unnoticed drug reactions are observed. There may be breed specific or individual differences in susceptibility to adverse reactions, there may be incompatibility with feed or other drugs used at the same time, there may be chance observations of previously unknown drug effects.

c. Living/Management Conditions of Target Species -

These conditions vary not only from species to species but also within the same species. Individual companion animals, feedlot cattle, beef cow/calf herds, dairy herds, are good examples for the diversity of the animals involved.

d. The Type of Parasite -

The plans for clinical trials will vary with the affected parasite as to timing, location, efficacy evaluation; with differences in seasonal and geographical occurrences; with the difficulty to diagnose. Liver flukes, gastrointestinal nematodes in cattle, heartworms in dogs, lungworms in bighorn sheep are examples.

Not only do different parasites require consideration of their life cycles for appropriate study design. Different populations of the same parasite may also differ. Resistance of parasites to certain chemicals is an example.

e. The Type of Product -

The formulations of anthelmintics are increasingly varied: oral liquids or pastes, injections, spot-ons, boluses or tablets, feed formulations, sustained release formulations.

A formulation which works well in the laboratory or in limited numbers of animals may be impractical to use or pose other problems under field conditions.

The discussion of variables to be considered in clinical trials with anthelmintics can be summed up by saying that there should not be a rigid cookbook recipe in which each box has to be checked to produce a valid study. Different designs can produce valid results depending on the variables addressed in a specific study.

We found it helpful to have some standard procedures written up for the initiation and performance of clinical trials. A possible sequence of events for setting up a trial may be:

- o Purpose or objective of the study is identified.
- o Drug supply is formulated.
- o A monitor is appointed. A decision is made how the study will be monitored. Studies with new compounds, new dosage forms with a new investigator and those which are intended to support claims will require closer monitoring than others.
- o A suitable investigator is identified and the test site evaluated.
- o The investigator must be capable of doing the study, must have the needed type and number of animals available for the study, must be in the desired location for a trial.
- o A protocol is drafted and discussed internally and then with with the investigator. The discussion includes suitable statistical design.
- o The appropriate format for reporting the results of the study is selected. Some studies are facilitated by the use of report forms, others may be easier reported in a different way.
- o Drug supply is packaged and labeled according to design (blind, double-blind, open study, placebo).
- o Pertinent government regulations including withdrawal times must be pointed out to the investigator and discussed as applicable.

- o An agreeable protocol is signed.
- o FDA is notified (if needed).
- o Drug samples are shipped.
- o Records of drug shipments are kept.
- o The study must be monitored.
- o Animals and drug samples must be accounted for.
- o The final report is checked for accuracy and compared to raw data. The final report is discussed with the investigator if he issues it. We found it advantageous to complete all reviews and checks immediately after the trial has been completed even though the report may not be used right away.

We use a checklist to keep track of these things. It is attached to the cover of each study folder.

Whatever the design, whatever the objective, some basic conditions have to be met to render a clinical trial useful. They are the same as for any clinical trial:

- a. Preset objectives
- b. Predefined parameters
- c. Suitable protocol
- d. Suitable investigator
- e. Follow-up
- f. Sufficient instructions for investigators
- g. Complete records of all events related to the study, including information about animals that got sick or died during the study. The records kept may differ with the target species involved or with various objectives. Studies with companion animals (dogs, cats, horses) emphasize individual animals and individual reports; studies with food producing animals (cattle, swine, sheep and so on) emphasize the herd and may require only herd records with individual worm counts.

- h. Results must relate to the objectives. The study must have been conducted according to protocol. The results may have to be interpreted to answer the objectives of the study.
- i. Conduct and records must meet possible government regulations where they are applicable.
- j. The study must be presented in a final report that reflects objectives and results, as needed with statistical analysis.

One major restraint is also the same for all clinical trials with anthelmintics: the studies have to be economically feasible. Expenses for studies in animals must be reasonable relative to the expected benefits.

#### Literature:

- (1) Powers, K. G., et al. (1982): World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) guidelines for evaluating the efficacy of anthelmintics in ruminants (bovine and ovine). *Vet. Parasitol.* 10:265-284.