

## **Biology of Anthelmintic Resistance: These Ain't Your Father's Parasites**

Ray M. Kaplan, DVM, PhD, DipACVM, DipEVPC  
College of Veterinary Medicine  
University of Georgia, Athens, GA

### **Introduction**

Anthelmintic resistance is defined as a heritable genetic change in a population of worms that enables some individual worms to survive drug treatments that are generally effective against the same species and stage of infection at the same dose rate. In practical terms anthelmintic resistance is present in a population of worms when the efficacy of the drug falls below that which is historically expected, when other causes of reduced efficacy have been ruled out. Parasitic nematodes have many biologic and genetic features that favor the development of drug resistance. Short life cycles, high reproductive rates, rapid rates of evolution, and extremely large population sizes combine to give many parasitic worms an exceptionally high level of genetic diversity. This leads to certain worms having gene mutations that reduce their susceptibility to the drug.

Amplification of resistance within a worm population to clinically relevant levels is a slow and gradual process, requiring numerous generations under drug selection (usually taking several to many years). Thus, from a practical perspective, the genetic phase of resistance develops slowly over time during which it is impossible to detect, but then increases very rapidly in its later phase, where it is then perceived as a clinical event. This has great clinical relevance because resistance can transition from undetectable, to clinically important levels over a very short period of time. Consequently, unless a surveillance program is in place that closely monitors the effectiveness of drug treatments over time, resistance will not be noticed clinically until levels of resistance are extremely high. There is also very strong evidence that once resistance is diagnosed as a clinical problem “reversion” to susceptibility likely will never occur.

### **The Scope and Prevalence of Resistance**

For many years, worms were controlled in small ruminants by the frequent use of anthelmintics, and this approach was quite effective. However, we now know that this strategy has turned out to be shortsighted and unsustainable. The prevalence of multi-drug resistant gastrointestinal nematodes (GIN; particularly *Haemonchus contortus* but also others) is extremely high any we are at risk of having no effective anthelmintics to use in the near future. Prior to 2000, there was little data on the prevalence of anthelmintic resistance in the US. There had been a few published reports over the years, but the state of the problem was unknown. In an initial collaboration between University of Georgia and Fort Valley State University, goatherds at the respective institutions were tested for resistance against multiple anthelmintic drugs. To our great surprise, at both sites *H. contortus* were multiply resistant to all 3 available drug classes (benzimidazoles, avermectins, levamisole); only moxidectin was effective but it had never been

used at either farm (Terrill et al., 2001). The results of this study raised serious concerns and led to a larger study on 18 goat farms in Georgia. This larger study confirmed the serious nature of the problem; >90% of farms had resistance to both albendazole and ivermectin and 1/3 had resistance to all 3 major drug classes (plus levamisole) (Mortensen et al., 2003). These findings pointed to the severity of the problem and served as an important impetus to the development of further collaborations, which ultimately contributed to the formation of the SCSRPC (which later became the ACSRPC). The SCSRPC then conducted a 46-farm region-wide study throughout the southern US investigating the prevalence of anthelmintic resistance on both sheep and goat farms (Howell et al., 2008). In that study, *H. contortus* from 45 (98%), 25 (54%), 35 (76%), and 11 (24%) farms were resistant to benzimidazole, levamisole, ivermectin, and moxidectin, respectively. Resistance to all 3 classes of anthelmintics was detected on 22 (48%) farms, and resistance to all 3 classes plus moxidectin was detected on 8 farms (17%). Thus on almost 20% of all farms tested, resistance was detected to all available anthelmintics; a situation referred to as “Total Anthelmintic Failure”. A more recent study performed by some ACSRPC members from 2007-2009 in the mid-Atlantic region found a further escalation of moxidectin resistance; 39% of farms had resistance (Jackson-O'Brien, submitted).

The rapid increase in moxidectin resistance is not surprising given the fact that ivermectin and moxidectin are closely related drugs that have the same (or very similar) mechanisms of action and resistance; resistance to one drug in this class confers resistance to all of them. The reason that moxidectin remains effective against ivermectin-resistant worms appears to be simply a matter of potency. Moxidectin is just a more potent drug against *H. contortus*, so that therapeutic doses are still capable of killing worms that have become resistant to ivermectin. Unfortunately, this efficacy has proven to be short-lived, therefore use of moxidectin must be carefully monitored and managed to maintain its efficacy. The reality is that moxidectin is no longer effective on a high percentage of sheep and goat farms in the eastern and southern US.

### **New Drugs and the Future of Parasite Control Using Anthelmintics**

One bright spot in this gloomy situation is the recent discovery of a novel anthelmintic class (amino-acetonitrile derivatives; AAD) (Kaminsky et al., 2008) and its introduction as Zolvix® (Monepantel) by Novartis in New Zealand, Australia, and several European countries. It is not known when or even if the FDA will approve Zolvix, but one could reasonably expect Zolvix will be approved and sold in the US in the relative near term. However, excitement regarding this new anthelmintic (the first new anthelmintic drug class for use in livestock introduced in more than 30 years) should be tempered by the lessons learned regarding the development of resistance to all drugs. Thus, if and when this new drug is approved, it must be used carefully and sparingly to guard against the rapid development of resistance.

Clearly then, major changes need to be made in the way that GIN control is practiced on many farms. Anthelmintics can no longer be thought of as an inexpensive management tool to be used as needed to maximize animal productivity and maintain herd health. Instead they must be thought of as extremely valuable and limited resources that are not readily renewable or replaced. We must balance our desire to maximize animal health and productivity with the reality that effective long-term control of *Haemonchus* will only be possible if anthelmintics are used less frequently, as well

as intelligently, with prevention of resistance as a goal. To address this issue, a concept referred to as ‘Smart Drenching’ has been introduced. Smart drenching is an approach whereby we use the current state of knowledge regarding host physiology, anthelmintic pharmacokinetics, parasite biology, dynamics of the genetic selection process for resistance, and the resistance status of worms on the farm to develop strategies that maximize the effectiveness of treatments while also decreasing the selection of drug resistance. One of the most important aspects of smart drenching is a selective treatment approach based on the use of FAMACHA<sup>®</sup>. These topics will be addressed in other papers presented at the meeting.

## Diagnosis of Anthelmintic Resistance

Before developing an effective control program for *Haemonchus* or any other GIN parasite, it is extremely important to know if resistant worms are present on a particular property, and if present, to which drugs. This can only be done 2 ways: (1) by performing a fecal egg count reduction test; or (2) by performing an *in vitro* larval development assay (LDA). The FECRT is the most readily available means for resistance diagnosis since it can be performed on any farm; but this test is labor intensive and requires performing many fecal egg counts making it expensive and inconvenient to perform. An alternative to the FECRT is the LDA (DrenchRite<sup>®</sup>), however, the test can only be performed in a specialized parasitology diagnostic lab. A single DrenchRite test can detect and measure resistance to benzimidazoles, levamisole, ivermectin and moxidectin from a single fecal sample. The Kaplan laboratory currently offers this test for a fee (\$450). This cost reflects the significant equipment and supply needs, as well as the great deal of technical expertise and labor required to perform the DrenchRite assay. [Requests for information about the DrenchRite test and current pricing should be sent to Sue Howell at \[jscb@uga.edu\]\(mailto:jscb@uga.edu\).](#)

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