

Responding To The Emergence of Multiple-Drug Resistant *Haemonchus contortus*: Smart Drenching and FAMACHA[®]

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Introduction

There are many important diseases of sheep and goats, but none are as ubiquitous or present as direct a threat to the health of goats as internal parasites. Control of internal parasites is therefore of primary concern in any small ruminant health management program, and is critical to profitability. Gastrointestinal nematodes (GIN) that infect sheep and goats include *Haemonchus contortus*, *Trichostrongylus colubriformis*, *T. axei*, *Teladorsagia (Ostertagia) circumcincta*, *Cooperia* spp., *Oesophagostomum*, *Trichuris ovis*, *Strongyloides papillosus*, and *Bunostomum*. Although all of these parasites can contribute to the overall problem of gastrointestinal parasitism, it is the highly pathogenic blood-sucking parasite *H. contortus* that by far is the most prevalent and important in most regions of the US, and especially in the southern states.

Diagnosis of haemonchosis is made based upon the characteristic clinical signs of anemia, submandibular anemia, weight loss, and ill thrift along with finding large numbers of eggs in the feces. Female *Haemonchus* produce approximately 5,000 eggs per day and goats can be infected with thousands of these worms. This results in tens to hundreds of thousands of eggs being shed onto pasture by each animal each day. Because the life cycle is so short (< 3 weeks), this cycle of infection - pasture contamination - reinfection - more pasture contamination - can rapidly transform pastures into very dangerous places for goats. This is especially true in a warm environment such as Georgia, because transmission of *H. contortus* occurs virtually year-round.

As is the case for most parasitic diseases, haemonchosis is most severe in young animals during their first year on pasture. However, since immunity to GI nematodes in goats is slow to develop and is incomplete, even mature goats are at considerable risk. Furthermore, any one or combination of a number of factors such as poor nutrition, concurrent disease, stress, overstocking, or pregnancy/lactation can cause a loss of immunity to parasites. It is well established that ewes and does lose much of their protective immunity to GIN around the time of kidding/lambing (-2 to +8 weeks) causing the number of parasites infecting the does to increase. Subsequently, parasite egg production and contamination of the environment with infective larvae increases, creating a dangerous situation for the highly susceptible young kids. This phenomenon, known as the periparturient rise (PPR) is an extremely important part of the epidemiology of *Haemonchus* and must be considered when designing control programs.

Anthelmintics Used in the Control of Gastrointestinal Nematodes

The number of FDA-approved drugs available for use in the treatment of haemonchosis (and other gastrointestinal parasites) in goats is severely limited. Currently only 4 drugs are approved for use in goats: morantel (Rumatel Medicated Premix-88®); thiabendazole (TBZ: Omnizole®, others); fenbendazole (FBZ: Safe-Guard®, Panacur®) and phenothiazine (Feno-Drench Suspension®), with thiabendazole no longer marketed. This list is further limited in usefulness since drug resistance to benzimidazoles (TBZ, FBZ, and related compounds) and phenothiazine is very common. Other unapproved drugs that are effective for the treatment of gastrointestinal parasites (if not resistant) in goats include: ivermectin (Ivomec®), doramectin (Dectomax®), moxidectin (Cydectin®), albendazole (Valbazen®), other benzimidazoles, and levamisole (Tramisol®, Levasol®). In sheep, ivermectin, albendazole and levamisole are FDA approved and moxidectin is an approved product for sheep in much of the world (but not the US) so extra-label use is less of an issue. However, in goats extra-label use is important because use of drugs other than what is indicated on the label is legally restricted and improper usage could lead (in theory) to regulatory action. The FDA does allow limited extra-label use of drugs, but this use is an exclusive privilege of the veterinary profession and is only permitted when a *bona fide* veterinarian-client-patient relationship exists and an appropriate medical diagnosis has been made (Anonymous 1992). Because effective control of internal parasites of sheep and goats can usually only be accomplished with these extra-label drugs, involvement of a veterinarian in the implementation of a parasite control program is not only advisable but is legally required.

When using drugs extra-label in goats it is extremely important that the sheep or cattle (label) dose is **not** used. Goats metabolize anthelmintic drugs much more rapidly than other livestock and require a higher dosage to achieve proper efficacy (Reinemeyer and Pringle 1993; Hennessy 1994). A rule of thumb is that goats should be given a dose 1.5 – 2 times higher than for sheep or cattle. A 1.5X dose (12 mg/kg) is recommended for levamisole, because a 2X dose is approaching a level that may be toxic in goats. For all other drugs it is recommended that a 2X dose be given. Because of the risk of toxicity with levamisole, it is recommended that it only be administered orally and that individual goats be weighed prior to treatment to determine the appropriate dose (Craig 1996).

Ivermectin and doramectin are avermectin drugs that have excellent efficacy against all stages of parasites in the host (if not resistant), and also have persistent activity when given by parenteral administration. Because doramectin has a much longer persistence but no significant improvement in efficacy compared to ivermectin, it will select for resistance more rapidly. Since resistance to either ivermectin or doramectin confers resistance to the other, it is my opinion that doramectin should not be used in goats for nematode control. However, doramectin injectable may be the treatment of choice for sheep scab (*Psoroptes ovis*) because its long persistence will clear the infection with a single treatment. Moxidectin, a milbemycin, is a very closely related compound with similar spectrum of activity that is more lipophilic than the avermectins and therefore has an even longer persistent activity (Hennessy 1997). Moxidectin is also more potent against many nematodes and therefore will often kill worms that are resistant to the avermectin drugs. Moxidectin is currently marketed in the U.S. only as a pour-on for cattle. Pour-on anthelmintics are generally poorly absorbed in small ruminants and have a low bioavailability, so they should never be used by that route. It is recommended that Cydectin pour-on be administered only by oral drench (0.4 mg/kg). However, moxidectin has an improved pharmacokinetic profile in goats when administered by injection. When the injectable moxidectin product for cattle becomes available in the near future, the injectable route will be the preferred route of administration. Nevertheless, use of moxidectin

should be minimized and used only with careful consideration (see below).

Anthelmintic Resistance: An Emerging Problem That Is Changing Our Approach For Controlling *Haemonchus* In Small Ruminants

Only a few years ago, recommendations for control of *H. contortus* in goats were based on the premise that anthelmintics should be used in a strategic manner to maximize animal productivity. This approach was used because it is known that subclinical parasitic infections are responsible for significant economic loss; once clinical disease is noticed in a group of animals much economic loss in terms of animal productivity has already occurred. Parasite control was therefore aimed at preventing animals from becoming highly parasitized, thereby maximizing productivity. Key to the success of this program was the availability of inexpensive and effective anthelmintics, since this approach required the frequent use of these drugs. We now know that this strategy has turned out to be shortsighted and unsustainable. The prevalence of multi-drug resistant *H. contortus* is extremely high any we are at risk of having no effective anthelmintics to use in the near future. In 2001, we published the first report of multiple-drug resistant *H. contortus* to all 3 available drug classes in the U.S. (moxidectin remained effective) (Terrill, Kaplan et al. 2001) and this past year we diagnosed the first case of total anthelmintic failure in the US (resistance to all available anthelmintics) (Kaplan 2005, unpublished). In 2001 we also completed the largest U.S. study to date on the prevalence of anthelmintic resistance in GIN in goats. Ninety percent of all farms tested in Georgia had *H. contortus* resistant to both ivermectin and albendazole. A further 30% of farms had *H. contortus* that were resistant to levamisole (Mortensen, Williamson et al. 2003). Moxidectin was the only drug effective on all farms, meaning that on 30% of farms it was the only drug that was fully effective. However, the problem of resistance continues to worsen; a follow-up study performed in 2003 demonstrated that 50% of farms tested with a history of moxidectin use over the previous 2 -3 years had moxidectin-resistant worms (Kaplan, unpublished).

This finding is not surprising given the fact that ivermectin and moxidectin are closely related drugs that have the same mechanisms of action and resistance; resistance to one drug in this class confers resistance to all of them.(Shoop, Haines et al. 1993; Molento, Wang et al. 1999). Dose-titration studies have demonstrated that the same resistance ratios (dose required to kill resistant worms:dose required to kill susceptible worms) exist for ivermectin and moxidectin. Therefore, ivermectin-resistant worms are technically also moxidectin-resistant. The reason that moxidectin remains effective against ivermectin-resistant worms is simply a matter of potency. Moxidectin is just a more potent drug 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 managed to maintain its efficacy. Moxidectin is highly persistent in animal tissues, preventing the establishment of IVM-sensitive (IVM-S) *H. contortus* in sheep for 35 days (Abbott, Cobb et al. 1995; Kerboeuf, Hubert et al. 1995). We recently reported the results of a study in goats that demonstrated that although moxidectin had 100% efficacy against IVM-resistant (IVM-R) adult worms, incoming IVM-R L₃ infective larvae were only killed for a few days following treatment (Kaplan and Ware 2001). Since the persistent activity of moxidectin prevents IVM-S L₃ from establishing for up to 5 weeks, treatment with moxidectin will allow goats to become infected with a pure IVM-R population of worms over an approximately 4-week period. This will likely result in a rapid accumulation of IVM-resistant genes within a population of parasites, further accelerating the selection for resistance.

Making matters worse, the anthelmintic market for small ruminants is deemed too small

by the pharmaceutical companies to justify the great cost associated with new drug discovery and development (Geary, Sangster et al. 1999). It is extremely unlikely, therefore, that new anthelmintics with novel modes of action will be developed and marketed in the US in the foreseeable future (Hennessy 1997). This is without a doubt a severe and important problem that directly threatens the viability of the sheep/goat industry. Clearly then, major changes need to be made in the way that nematode control is practiced. Small ruminant parasitologists are now calling for a shift in the paradigm of thought used to control *H. contortus* in goats. Anthelmintics can no longer be thought of as an inexpensive management tool to be used as needed to maximize animal productivity, but instead must be thought of as an extremely valuable and limited resource. We must balance our desire to maximize goat health with the reality that effective long-term control of *Haemonchus* in goats will only be possible if anthelmintics are used 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[®].

Diagnosis of Anthelmintic Resistance

Before developing an effective control program for *Haemonchus*, 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 (FECRT; see table 2); or (2) by performing an *in vitro* larval development assay (LDA). The FECRT is presently the most definitive means of determining whether resistance is present on a particular property, but this test is labor intensive and therefore expensive to perform. An alternative to the FECRT is the LDA (DrenchRite[®]), however, the test is not suited for in-clinic use and can only realistically be performed in a parasitology diagnostic lab. A single DrenchRite test can detect resistance to benzimidazole (BZ), levamisole (LEV), BZ/LEV combinations, and ivermectin anthelmintics from a single sample. The DrenchRite assay does not directly test for moxidectin resistance, but recent studies in my laboratory have established reliable resistance ratios based on the ivermectin dose response that enable us to accurately diagnose moxidectin resistance using this test. In the DrenchRite assay, nematode eggs are isolated from feces and placed into the wells of a microtiter plate containing growth media and varying concentrations of anthelmintic. The concentration of anthelmintic required to block development of nematode larvae is related to the *in vivo* efficacy of the drug. My laboratory currently offers this test on a limited basis for a fee \$175. This cost reflects the great deal of labor required to perform the DrenchRite assay. Due to funding received from a SARE grant; beginning in September 2005 we will have an increased capacity for performing these tests. Requests for information about the DrenchRite test should be sent to Sue Howell <showell@vet.uga.edu>.

When considering the cost of the test it is important to realize that only one DrenchRite test performed on a pooled fecal sample from 10-20 goats/sheep is needed per farm, and all 3 major drug classes (including moxidectin) are tested in each assay. This is in comparison to the FECRT, where before and after treatment fecal egg counts (FEC) must be performed on individual animals from different treatment groups. Since FEC vary greatly, for the data to be useful at least 6 and preferably 10 – 15 animals should be used per group. If less than 10 animals are used per group it is necessary

to perform pre-treatment FEC so that treatment groups can be balanced by level of infection. If >10 animals are included in each group, it is probable that groups will be sufficiently balanced to obtain useful data. An untreated control group should always be included, so if 4 drugs are tested, 90-150 McMaster FEC must be performed. Therefore, even when excluding the time and labor costs of conducting the study, the cost of a FECRT is many times greater than a DrenchRite.

Smart Drenching

There are some specific strategies that can and should be used to maximize the effectiveness of treatments and to prevent the development of anthelmintic resistance. Some of these are directly related to the concept of smart drenching, while others relate to general management practices. The implementation of these strategies may vary considerably depending upon: (1) the primary parasite species that needs to be controlled, (2) the level and spectrum of resistance already present in a region (or farm), and (3) regional/local management systems that are used. However, there are some general guidelines that are useful in almost all circumstances and these are listed below. Finally, FAMACHA[®] must be regarded as a centerpiece of any worm control program where *Haemonchus contortus* is the primary problem.

FAMACHA[®] -- Selective rather than whole-herd treatment: This is the newest approach to smart drenching and is probably the most important component of a program designed to delay the development of resistance. The reason for this is that the most important factor affecting the rate of selection of anthelmintic resistance is the size of the unselected proportion of the population (Sangster 1999; Van Wyk 2001). This unselected population, referred to as refugia, provide a pool of sensitive genes, thus diluting the frequency of resistant genes in a population of worms. In practical terms, refugia would be all the infective larvae already on pasture at the time of treatment and the worms in hosts that are left untreated with anthelmintic. The larger the refugia, the slower the evolution of resistance. Parasitologists now believe that one of the major factors leading to the rapid and widespread development of anthelmintic resistance is the common practice of treating all animals in the herd at one time. This practice leaves no worms in refugia; the only eggs to hit the pasture for several weeks following treatment are from those worms that survived treatment. Furthermore, if treatments are given when few infective larvae are on pasture, (early in grazing season or during drought), then eggs shed by the resistant worms that survived the treatment are not greatly diluted. This gives these resistant larvae an even greater chance of re-infecting their hosts.

We know that worm burdens are not evenly distributed in animal populations; 20% of the animals harbor about 80% of the worms. These 20% are primarily responsible for contaminating the environment with infective larvae for all the other animals. If we could identify those 20% and treat only those animals, we could control the parasites, save money by reducing the number of treatments given on a herd basis, and greatly lessen the selection for resistance by maintaining a large refugia. The question then becomes, how can we accurately identify those animals that require treatment?

Recently, a new clinical on-farm system for classifying animals into categories based upon level of anemia has been developed in South Africa. Since anemia is the primary pathologic effect from infection with *H. contortus*, this system called FAMACHA[®], can be an effective tool for identifying those animals that require treatment. To use FAMACHA[®], farmers observe the color of ocular mucus membranes and compare this color to a laminated card with illustrations of eyes from sheep at different levels of anemia. The card is calibrated into 5

categories: 1 = red, non-anemic; 2 = red-pink, non-anemic; 3 = pink, mildly-anemic; 4 = pink-white, anemic; 5 = white, severely anemic. In South Africa, FAMACHA[®] has proven to be a very accurate means of identifying sheep that require treatment, however, accuracy is reduced in goats. Recently, several of my colleagues and myself completed a study to validate the use of FAMACHA[®] in sheep and goats in the southern U.S. (Kaplan, Burke et al. 2004). Based on this study we have developed a set of guidelines for its use (see FAMACHA[®] Information Guide at www.scsrpc.org). It is important to keep in mind, however, that as we gain experience with this method our recommendations may change.

Based on the results of this study for both sheep and goats in the southern US and the US Virgin Islands, it appears that treatment could be safely withheld until animals score as 4s or 5s as long as animals are in good body condition and good overall general health, are examined frequently (e.g., every 2 weeks) and good husbandry is used to identify animals in need of treatment (e.g., unthrifty, anorexic, lagging behind, bottle jaw) between FAMACHA[®] examinations. When a PCV cutoff of ≤ 15 was used as critical value for necessitating treatment, and all animals scored as 4s and 5s were treated, the percentage of false negatives (animals that had a PCV ≤ 15 but were scored as a 3, 2 or 1) was 0.5% and 0.6% for sheep and goats, respectively. At this level, death from anemia would be a very rare occurrence as long as the suggestions mentioned above were used to identify these few animals in need of treatment that were not detected with FAMACHA[®]. Using this approach the number of anthelmintic treatments administered will be greatly reduced, resulting in diminished selection pressure for resistance and a concomitant reduction in drug costs. In our study, if only animals with eye scores of 4 and 5 were treated, 14% of sheep and 31% of goats would have received anthelmintic. However, it is recommended that this scheme should only be applied to adult animals. Lambs and kids have comparatively small blood volumes and can progress rapidly from moderate to severe anemia. This precaution should also be extended to ewes and does extending from the periparturient through the lactation period, since these animals have decreased immunity to GIN and high nutritional demands. These and other animals that may be stressed by disease or poor body condition should always be treated if scored as 3s.

An alternative approach could be to treat all 3s, 4s and 5s. This will result in many more treatments being given to non-anemic animals, but will virtually eliminate the possibility that an anemic animal will fail to receive treatment. Also, because many animals scored as 3s still have high FEC, treating this group will greatly reduce egg contamination of pastures. Although many more treatments will be given, significant refugia will be maintained and the evolution of anthelmintic resistance should still be slowed considerably. On farms where resistance testing shows that several drugs are still effective, treating all 3s, 4s and 5s would be a safer approach and will result in better worm control. Many animals will still be left untreated supplying a significant level of refugia.

On farms where low to moderate levels of resistance has been diagnosed to one or more drugs (60-95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less-effective" drugs either singly or in combination on all animals scored as 3s. Using drugs that are less effective in this group should not cause clinical problems to develop because the few 3s that are moderately anemic and in need of treatment, should receive a sufficient reprieve from infection until the next FAMACHA[®] examination, and the majority of the 3s which are not anemic do not really need to be treated. This strategy will help preserve the efficacy of the drugs that are still fully effective by saving them only for the 4s and 5s, and also will help to minimize egg contamination of pastures.

In addition to the benefits of reducing drug costs and delaying the development of anthelmintic resistance, use of FAMACHA[®] can also help to improve the genetic resistance of individual herds or flocks (Bath, Hansen et al. 2001). Analyses of data in our study revealed highly significant correlations between PCV, eye score, and FEC. It has been established previously that host resistance to infection with *H. contortus* measured on the basis of FEC and PCV is a moderately heritable trait (Albers, Gray et al. 1987), and it has been demonstrated that the same animals tend to exhibit the highest FEC and lowest PCV on each occasion that they are measured (Barger and Dash 1987). Importantly, data from recent investigations examining the heritability of resistance and resilience of Merino sheep to infection with *H. contortus* indicate a high heritability for the clinical estimates of FAMACHA[®] scores (Van Wyk and Bath 2002). Since it can be expected that the same animals will require frequent treatments, and this trait of parasite susceptibility will be passed to the next generation, FAMACHA[®] can be a very useful tool for identifying animals to be culled. Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance and/or resilience of the herd or flock to *H. contortus*. Such progress could never be made using traditional anthelmintic treatment approaches.

While it appears simple and straightforward to examine ocular mucous membranes and assign animals to the proper category, experience in South Africa and here in the US has shown that training and experience is required to use this system effectively. It is critical that users of FAMACHA[®] receive proper training and understand the risks of incorrect use of this system (e.g. animal mortalities) and necessary precautions that should be taken. It must also be remembered that there are several other important gastrointestinal (GI) nematodes that cause disease besides *Haemonchus contortus*. In warm climates they tend to have minor importance relative to *H. contortus*, but in cooler climates they can be very important. FAMACHA[®] is only useful to detect animals in need of treatment due to infections with *H. contortus* and CANNOT be used to detect worm infections with these other GI worms. In Kentucky, *Trichostrongylus colubriformis* and *Teladorsagia (Ostertagia) circumcincta* can be important small ruminant pathogens, especially during the cooler months of the year. It is important not to forget about these other worms, and this is an important reason to periodically monitor FEC even when using FAMACHA[®].

Veterinarians can get more information about FAMACHA[®] by sending an email to famacha@vet.uga.edu or by visiting www.scsrpc.org. FAMACHA[®] is distributed under the auspices of the South African Veterinary Association. Professor GF Bath (project coordinator for FAMACHA[®] in South Africa) has requested that distribution in the US be made only through the SCSRPC via the laboratory of Dr. Kaplan (University of Georgia) and that FAMACHA[®] cards are only to be sold directly to veterinarians or other trained animal health professionals. These individuals are expected to provide training in the proper use of the FAMACHA[®] system prior to re-selling the cards.

Know the resistance status of the worms infecting the herd: With the prevalence of resistance so high, it is critical that anthelmintic efficacy be determined on each farm and be monitored every 1 to 2 years. Even when the prevalence of resistance is high, there are some farms where drugs are still effective. These farms would gain considerable benefit by using these drugs. Therefore, drugs should not be excluded from use just because resistance is common. On the contrary, one does not want to use drugs that are ineffective. The only way to determine this is to perform a test.

When using the highly recommended FAMACHA[®] method, it becomes even more important to know the resistance status of the farm because animals are not treated until they show signs of

anemia. If anthelmintic treatments had been applied at frequent intervals prior to using FAMACHA[®] resistance may have been masked, especially if a rotation of drugs was used. In contrast, if treatment is withheld until animals are anemic and a drug that has moderate to poor efficacy due to worm resistance is used, then deaths may occur. This is a prime example of why training is required prior to using the FAMACHA[®] system.

Keep resistant worms off the farm: Anthelmintic resistant worms can come from only two sources; either they are selected for by drug treatment or they are purchased. It is therefore important for sheep and goat producers not to buy resistant worms. All new additions to the herd or flock should be quarantined in a dry lot (without any grass) or on concrete and aggressively dewormed upon arrival. Upon arrival, I recommend that all new additions be held without feed for 24 hours, and then dewormed sequentially with moxidectin, levamisole, and albendazole. After 14 days a FEC should be performed and the animal should only be allowed to enter the herd if the fecal is negative. If a 14-day quarantine is not possible, animals should be confined to pens for a minimum of 48 hours following treatment before being moved to pasture. However, this is a risky approach. After the animal is released from quarantine, it should be placed on a pasture previously grazed by sheep or goats (large refugia) and should NEVER be placed on a clean or safe pasture.

Administer the proper dose: Every dose of anthelmintic should be given with the goal of maximizing the killing of worms. Several studies have demonstrated that sheep/goat producers often underestimate the weight of their animals and therefore underdose their animals. Underdosing exposes worms to sublethal doses of drug, which increase the selection for resistance. Animals should be weighed individually or dosed according to the heaviest animals in the group (except for levamisole in goats where overdosing can be risky) and dosing equipment should be frequently checked for accuracy.

Utilize host physiology to maximize drug availability and efficacy: Anthelmintic efficacy is directly related to the duration of contact between drug and parasite. With all other factors being constant, by simply extending the contact time, drug efficacy is improved. Knowledge of host physiology can therefore be used to increase drug efficacy. When orally treating a ruminant it is critical that the full dose lodges in the rumen. Once in the rumen, the duration of drug availability as it is absorbed from the rumen and flows to more distal sites of absorption is largely dependent on the flow-rate of the digesta (Hennessy 1997). Since rumen volume remains relatively constant, there is an inverse relationship between feed intake and digesta residence time. Simply restricting feed intake for 24 hours prior to treatment decreases digesta transit and increases drug availability and efficacy. This is not a theoretical issue - it has been demonstrated in both pharmacokinetic studies and field efficacy trials where this strategy significantly increased the efficacy of fenbendazole against benzimidazole field-resistant strains of GI nematodes (Hennessy 1997).

Proper technique when drenching animals is also very important. All anthelmintics administered orally should be delivered over the back of the tongue. Presenting a drench to the buccal cavity, rather than into the pharynx/esophagus, can stimulate closure of the esophageal groove with significant drench bypassing the rumen (Sangster, Rickard et al. 1991). Absorbed drug concentrations may be higher initially, but are of such short duration that efficacy is reduced (Hennessy 1997). Special dosing syringes and extenders that attach to regular syringes are sold by several sheep supply companies and should be routinely used. Without any additional cost or effort, these 2 recommendations have the potential to significantly prolong the useful life of today's anthelmintics and should be used as a matter of course.

Split and repeat dosing: As mentioned above, increasing the duration of contact between drug and parasite can significantly increase efficacy. This also can be accomplished by administering 2 doses 12 hours apart. Repeat dosing can be used as an alternative to withholding feed, or even better, in addition to withholding feed. In a recent study, the efficacy of fenbendazole increased from 50% when administered as a single dose, to 92% when 2 doses were administered 12 hours apart (Zajac and Gipson 2000).

Dosing with two different drugs at same time: When drugs are still effective, treating with 2 drugs of different anthelmintic classes simultaneously can delay the development of resistance. Once resistance is present, treating with 2 drugs of different anthelmintic classes can still be of great benefit. Anthelmintics given together will produce a synergistic effect; significantly increasing the efficacy of treatment compared to the individual drugs. This synergistic effect is most pronounced when the level of resistance is low. Once high-level resistance to both drugs is present, the synergistic effect is unlikely to produce an acceptable efficacy.

Rotation of anthelmintics: Rotation is an overblown concept that gives farmers a false sense that they are actually doing something worthwhile in terms of resistance prevention. The common practice of rotating drugs with each treatment does not slow the development of resistance, and actually appears to increase the rate at which resistance develops by selecting for resistance to more than one drug simultaneously. When more than one anthelmintic class is effective, it may be advantageous to perform annual (slow) rotation. In a slow rotation a single anthelmintic should be used for an entire year, and a second drug used the next. Although a slow rotation has been generally accepted as beneficial for delaying resistance, there is no direct evidence for this. There are arguments now being made by some parasitologists that rotation should not be used. Rather, some recommend that an anthelmintic should be used until it is no longer effective and then drugs should be switched. The main rationale behind this approach is that it will become obvious when a drug no longer works so the farmer will always be aware of his/her situation. If a rotation is used, resistance develops slowly to all drugs and the farmer is unaware of this until multiple-drug resistance is a serious problem. Whether rotation is used or is not used, it is important to understand that rotation is NOT a replacement for proper resistance prevention measures. It also is worth noting that many farmers do not know what products are in which drug class. There are many drugs with different brand names that belong to the same drug class - rotation between different products within the same drug class will do nothing to slow down resistance. Rotation also becomes moot when only 1 drug is effective; a situation that is becoming increasingly common.

Recent computer models that examined the effects of various worm control strategies on anthelmintic resistance suggest that the most effective approach for delaying the selection for resistance is to treat simultaneously with 2 chemically distinct anthelmintics. Although expensive and not routinely practiced, this approach deserves further attention in light of the current situation. Unfortunately, to be truly effective in preventing resistance, this approach must be implemented while the number of resistant worms is extremely low (long before detectable levels). This situation rarely exists anymore.

Reduce the frequency of treatment through the use of sound pasture management: Good pasture management can also go a long way in preventing resistance by minimizing the dependence on dewormers. Anthelmintics alone will not successfully control parasites. Managing pastures so that safe grazing areas are available will permit animals to be moved to a safe area, reducing the number of treatments that are needed. It is important however, that the animals not be treated

immediately before the move to safe pasture unless a proportion of the animals are left untreated. Also, goats are natural browsers so browse areas should be used as much as possible. Parasite transmission is greatly reduced when goats are browsing because they are ingesting forage farther from the ground. Reducing stocking rates will decrease the number of parasites that sheep and goats are exposed to and will also improve the quality and quantity of forage available to the animals. Overstocking can often make control of *Haemonchus* nearly impossible. Also, using fewer, strategically timed treatments during high risk portions of the year i.e. young kids/lambs following weaning and lactating does around the time of kidding, in combination with the use of FAMACHA[®] will decrease the amount of exposure worms have to the drug and therefore significantly slow down the development of resistance.

Novel Non-Chemical Approaches

In response to the crisis posed by drug-resistant parasites, researchers and extension personnel who have the responsibility of providing parasite control advice to the small ruminant industry have come to realize that total reliance on chemical control for parasites is no longer a viable strategy, and new innovative schemes using sustainable approaches must be implemented. There are a number of new non-chemical technologies that will become increasingly important in anti-nematode control programs both in the short and long term future (Miller and Waller 2004). These include vaccines,(Knox, Redmond et al. 2003) nutritional supplementation,(Coop and Kyriazakis 2001) biological agents to destroy nematode larvae, (Larsen 1999) bioactive forages,(Athanasiadou, Kyriazakis et al. 2001) copper oxide wire particle boluses,(Chartier, Etter et al. 2000) and various genetic approaches. However, none of these by themselves is likely to provide an answer to the problems of parasite control. Instead an integrated approach that combines several of these novel methods together with limited but intelligent use of anthelmintics will be necessary.

Parasite vaccines remain an elusive goal and it will likely be many more years before effective vaccines become commercially available. Breeding for genetically resistant sheep has progressed at a slow pace, but offers great promise. Unfortunately, researchers have found that resistance to nematodes and production traits are often in selective conflict. Bioactive forages such as those containing condensed tannins may become part of an integrated approach to GIN control, but benefits in many studies were only marginal. However, other studies have demonstrated noteworthy results (Paolini, De La Farge et al. 2005; Terrill 2005, unpublished). This variability in results is likely due to the fact that different types of tannins, different forage species, and different means of delivery (e.g. hay, vs. grazing vs. green chop, vs. pellet; continuous vs. intermittent, etc.) all impact the effect of the tannin on the parasite and the host-parasite interaction. Additionally, tannins affect the different species of GIN differently. Copper oxide wire particle boluses have demonstrated good efficacy against *H. contortus* in some studies (Burke, Miller et al. 2004), but additional research is still required to determine proper dosage, treatment frequency, and potential negative health effects relating to copper toxicity. One of the leading non-chemical technologies that has received much attention in the past few years is the naturally occurring nematode-trapping fungus *D. flagrans*, which acts as a biological control agent. Spores of this fungus are grown on grain and fed to animals where they pass unchanged through the digestive tract and concentrate in the feces. After feces are deposited onto the pasture, the spores germinate forming hyphae that are able to trap and kill the developing larval stages of parasitic nematodes. Numerous studies have been done with most

showing positive benefits (Larsen 2000; Fontenot, Miller et al. 2003; Terrill, Larsen et al. 2004), although the degree of benefit has varied greatly between studies. However, problems in developing a practical and convenient means to administer the fungus have delayed development of a marketable product. This fungus remains commercially unavailable and it is unknown whether a product will be sold anytime soon.

Therefore, at the present time we are unfortunately left with few well tested options other than good management and intelligent chemical control with dewormers. However, veterinarians and small ruminant owners must be prepared to keep up to date with new developments that are certain to materialize in the next few years as these novel approaches are tested and validated. In the mean time, specific strategies exist that can and should be used to maximize the effectiveness of treatments and to prevent the development of dewormer resistance. Foremost, in most areas of the world dewormers can no longer be thought of as a relatively inexpensive management tool to be used as needed to maximize animal productivity. Instead dewormers must be thought of as extremely valuable and limited resources which should be used prudently. In response to this changing paradigm of dewormer use, new recommendations for parasite control have been proposed. The basis of this approach is to use the knowledge we have about the parasite, the sheep, and the drugs to develop strategies that maximize the effectiveness of treatments while also decreasing the development of drug resistance. The term “Smart Drenching” has sometimes been used to describe this approach to worm control.

Conclusion

The days of being able to control GIN in small ruminants by treating with anthelmintics at frequent intervals are nearing an end. Therefore, if anthelmintics are to remain a viable component of GIN control, a fresh ‘Smart Drenching’ approach will be needed. Due to the complexities of instituting such a program, successful implementation will only be possible with the help and active involvement of small ruminant veterinarians and other animal health personnel. Resistance to moxidectin has rapidly developed in the past few years and on some farms this drug has already become useless. Therefore on farms where moxidectin remains effective it should be reserved for life-saving purposes (4s and 5s, or just 5s on FAMACHA[®]), and should not be used for routine treatments unless there are no effective alternatives. Even where resistance exists to all drugs except moxidectin, less effective drugs may be used in animals with only a marginal need for treatment (e.g. 3s on FAMACHA[®]). Ultimately, GIN parasite control in small ruminants must be practiced with an eye to the future. It is quite likely that any new technologies or developments in non-chemical GIN control methods will be less effective than chemical control has been (prior to emergence of drug resistant parasites). Therefore, as novel non-chemical control modalities become available and widely applied, anthelmintics will still be required for life-saving therapy when control fails. Unless we dramatically change the ways we use anthelmintics, there may be no effective anthelmintics remaining when that time comes.

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