Pharmaceutical treatments of gastrointestinal nematode infections of sheep—Future of anthelmintic drugs

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ARTICLE INFO

Keywords:
Anthelmintic
Anthelmintic resistance
Nematode
Sheep

ABSTRACT

Various interacting factors have been identified to explain why health plans for nematode parasite control, based on conventional epidemiological knowledge and involving pharmaceutical treatments of their sheep hosts have become unsustainable. Of these, the emergence of anthelmintic resistance has had a major impact on the economics of sheep farming, necessitating fundamental management changes. This review focuses on the use of anthelmintic drugs for the control of gastrointestinal nematode infections in sheep, emphasising the need to develop sustainable strategies in the face of inevitable parasite evolution in response to exposure to anthelmintic drugs and other noxious stimuli, or favourable opportunities resulting from changing animal management and climatic factors.

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1. Introduction

Parasitic nematodes are thought to have evolved from free-living organisms that were present in oxygen-starved, benthic deposits as long as 1000 million years ago, becoming parasitic as their hosts then co-evolved during the past 350 million years (Sutherland and Scott, 2010). The biological success of parasitic nematodes depends in part on their long-term ability to coexist with their hosts in a manner, whereby the host provides the conditions required by the parasitic population, while the parasite does not compromise the host to an extent that would threaten the survival of its future generations. In relatively recent times, the evolutionary balance between parasites and, for example, their sheep hosts has been upset by domestication and the subsequent development of intensive livestock management practices, which create environments that are suited to the development and survival of free-living stages of the parasites, enhance sheep exposure to infective larvae, inadvertently alter the host innate or adaptive immune responses to infection and enable exposure to previously unrecognised parasitic nematode species or strains. Furthermore, these conditions may have affected different parasitic nematode species to differing extents, upsetting the equilibrium that may exist within the sheep host between different parasites (Mapes and Coop, 1973; Dobson and Barnes, 1995), affording a competitive advantage to some and allowing potentially pathogenic species to predominate.

Teladorsagia circumcincta, Haemonchus contortus, Trichostrongylus vitrinus or Trichostrongylus colubriformis and Nematodirus battus have evolved to become the major production-limiting nematode parasite species affecting sheep in temperate climates, their relative importance being influenced by regional and temporal differences in climate and sheep management. These parasites limit the productivity of susceptible animals: because of their direct feeding activities, removing nutrients from the ingesta; due to indirect effects on the immune response in their hosts (Greer, 2008), damaging the absorptive lining of the gastrointestinal tract; or, in the case of H. contortus, by feeding on blood. The net pathophysiological effects of these activities are inefficient feed utilisation, inducing a
state of relative protein deficiency, fluid and electrolyte or macroelement imbalances and anaemia, leading to clinical signs, such as reduced appetite, poor weight gains, diarrhoea and death. Overall, the greatest economic importance of nematode parasites is suboptimal productivity arising from continuous low-level exposure to infective larvae (Coop et al., 1982). Thus, the intensification of sheep production has necessitated control strategies for parasitic nematodes.

Parasitic nematodes can be controlled either by evasion or by suppression, primarily involving pharmaceutical treatments of their hosts. The simplest way in which to evade infective larval challenge is to manage sheep extensively, by adopting low stocking densities and co-grazing or browsing with other ruminant species on a variety of mature herbage plants. However, such management is not conducive towards economic meat, wool or milk production. Alternative evasive strategies are based on the principles that survival of infective larvae is limited, being negatively influenced by effects of increasing temperature and decreasing moisture on their microhabitat and that, while sheep are hosts to several of the same parasitic nematode species, cattle and deer are not. Thus, in regions such as northern United Kingdom which have temperate climates, pastures harbouring relatively low levels of infective larvae can be generated by the removal of susceptible sheep for a period of about 6 months, which can be conducive to economic productivity, whenever it is practical to finish naïve meat producing lambs quickly, thereby removing them early in the grazing season, or to utilise the fields for cattle grazing, forage conservation, or cereal production during the period when the sheep would be excluded. However, on most farms, the reasons for keeping sheep are to produce a marketable meat, wool or milk product from areas that are not suited to other forms of agricultural production or to manage areas for other environmental or non-agricultural purposes, such as grouse shooting. As a consequence, the grazing requirements of the sheep are high relative to those of cattle or the equivalent area taken up by cereal production, precluding the economic application of evasive management strategies as the sole method of parasitic nematode control, and necessitating the strategic use of pharmaceutical treatments of their sheep hosts with the aim of suppressing the size of the infective larval population (Barger, 1997). In fact, the development of anthelmintic drugs has enabled economic productivity in many situations where economic, intensive sheep production would otherwise have been untenable due to the effects of nematode parasites.

2. Anthelmintic drugs

Many chemical compounds and plant metabolites have toxic effects on nematode parasites, although most, including drugs such as sodium arsenite, tetrachloroethylene, carbon tetrachloride, carbon bisulphide, copper sulphate and nicotine sulphate, which were used as early, crude anthelmintic drugs, are potentially equally toxic to the parasites and to their sheep hosts. The introduction of phenothiazine in the 1940s (Gordon, 1945), followed by the discovery and development of the first tubulin-binding benzimidazole drug, thiabendazole, in the early 1960s (Borgers et al., 1975) enabled profitable sheep production in parts of the world where it had previously become untenable. This was followed by the introduction of: the first ganglion blocking imidazothiazole drug, levamisole, in the early 1970s (Coles et al., 1974); the first macrocyclic lactone drug, ivermectin, in the early 1980s (Turner and Schaeffer, 1989); the amino-acetonitrile derivative (AAD) drug, monepantel, in 2010 (Kaminsky et al., 2008); and the spiroindole drug, derquantel, in combination with abamectin (only in some southern hemisphere countries) in 2010 (Little et al., 2010). In addition, the salicylanalide derivative drugs, closantel (Dash, 1986) and nitroxynil, are available and have a narrow spectrum of activity against H. contortus.

Tubulin-binding drugs bind to tubulin proteins in the cytoplasm of the intestinal cells of nematodes, preventing polymerisation of tubulin to form microtubules (Borgers et al., 1975; Lacey, 1988). Microtubules form the structural basis of many cellular activities, including motility, secretion, co-ordination and glucose transport, thus susceptible nematodes die of starvation. Benzimidazole drugs are ovicidal, as well as inhibiting egg hatching of nematodes (Southcott, 1983). Ganglion-blocking agents act in different ways as cholinergic agonists and cell depolarisers at nematode nerve ganglia, causing rapid onset sustained muscle contraction and reversible spastic paralysis (Coles et al., 1974). Paralysed nematodes are dislodged into the intestinal lumen.

The mechanisms of action of the macrocyclic lactone drugs involve an increase in membrane permeability to chloride ions (Turner and Schaeffer, 1989), which is time dependent (Gill et al., 1991). Their known effects on nematode parasites include reduced pharyngeal pumping, paralysis of body muscles and effects on the uterus, leading to failure to feed, move or lay eggs, respectively. The main drug targets are considered to be glutamate- and γ-aminobutyric acid- (GABA) gated chloride channels, while non-specific targets of action, such as the P-glycoproteins (P-gp) involved with trans-membrane drug efflux pumps may also prove to be important (Blackhall et al., 2008).

The mode of action of the spiroindole drug, derquantel, involves binding to acetylcholine receptors, causing rapid muscle paralysis and death (Ruiz-Lancheros et al., 2011).

The mode of action of amino-acetonitrile derivative drugs has been investigated by forward genetic screening of drug resistant mutants of C. elegans and H. contortus and seems to involve a unique nematode-specific clade of acetylcholine receptor subunits (Kaminsky et al., 2008).

These anthelmintic drugs, when given at the recommended dose rates, have a wide safety margin to both sheep and the operator and are highly effective at removing most stages of susceptible nematode parasites from their host. Some drugs, in particular mebendazole, fenbendazole and levamisole, are not always effective against inhibited fourth stage larvae of the abomasal nematode parasites T. circumcincta and H. contortus (McKenna, 1974; Lancaster and Hong, 1977; Andrews, 2000), which may occasionally be of practical significance when ewes or lambs are treated during late autumn or winter (Sargison et al., 2007a).
3. Opportunities afforded by parasitic nematode lifecycles, epidemiology and biology for use of anthelmintic drugs

Various highly successful pharmaceutical nematode parasite control strategies have been developed, based on the fundamental principle that production losses due to nematode parasites arise primarily from the hosts’ immune responses to infective larval challenge, and the need to strike a balance between the levels of challenge that might impair animal performance and those required to enable the development of protective immunity (Coop et al., 1982). Pasture infective nematode larval contamination in the spring (predominantly with T. circumcincta in temperate regions) arises both from over-wintered infective larvae on pasture and from nematode eggs shed by recently lambed ewes (Wilson et al., 2008). The egg output of lactating ewes derives from nematodes, which overwintered as inhibited early fourth stage larvae or adults, and from completion of the lifecycle of overwintered infective larve ingested from pasture after lambing (Gibson, 1973). The relative importance of these sources of pasture larval contamination differs from year to year with different winter weather conditions and sheep grazing management, as well as between different regions, depending on the nematode genera involved. When ingested by naive lambs, these infective larvae give rise to adult nematodes, which accumulate over the summer months and contribute to subsequent pasture larval contamination, potentially leading to production limiting infections. Pharmaceutical treatments are most efficiently given with the aim of reducing the level of nematode egg shedding onto pasture, thereby suppressing the infective larval challenge to naive animals, and not surprisingly, most farmers have become dependent on frequent routine anthelmintic treatments of their sheep.

4. Reasons for failure of pharmaceutical control of parasitic nematodes

During recent years, suboptimal sheep productivity due to parasitic gastroenteritis has become commonplace, despite the adoption of blueprint nematode parasite control programmes involving the use of anthelmintic drugs. These problems have arisen due to a combination of factors, including effects of concurrent disease or management on anthelmintic drug pharmacokinetics, exemplified by the common failure of benzimidazole drugs to kill N. battus in scouring lambs, when the anthelmintic bioavailability may be reduced due to rapid flow of digesta through the intestines, and the emergence of anthelmintic resistance. Other factors may have led to inappropriate timing of anthelmintic treatments. For example, the evolution of parasites in response to climate change (Van Dijk et al., 2010), exemplified by the opportunities afforded to H. contortus by wetter and milder spring and autumn weather in northern Europe (Sargison et al., 2007a; Kenyon et al., 2009), the changing seasonal pattern of nematodirosis in the United Kingdom (Van Dijk and Morgan, 2010) and consequences of changes in farm and grazing management resulting from changing economics of sheep production (Sargison et al., 2002).

5. The inevitable evolution of anthelmintic resistance

T. circumcincta or H. contortus resistance to benzimidazole, imidazothiazole and/or macrocyclic lactone anthelmintics is now commonplace in many countries. Once resistance to an anthelmintic group has emerged within an individual sheep flock, the control of parasitic gastroenteritis using any of the drugs belonging to that anthelmintic group is compromised. Long-term reversion to susceptibility is unusual or, in all probability, does not occur within flocks. Multiple anthelmintic resistance is, therefore, a serious threat to economically sustainable sheep production (Blake and Coles, 2007), because it necessitates fundamental, often expensive, changes to animal management and compromises for the control of nematode parasites if it is allowed to reach a high enough level. While lowground farmers can change from uneconomic sheep production to cereal cropping in response to unsustainable nematode control, the options for many hill and upland farmers are limited. On most northern European sheep farms, the first indications of anthelmintic resistance are the failure of lambs to reach finished weights by late autumn, which may be combined with scouring and even deaths due to parasitic gastroenteritis, despite preventive anthelmintic treatments (Sargison et al., 2007b). However, anthelmintic resistance can result in clinically in-apparent, sub-optimal growth rates for some time before these overt signs of disease are seen (Barger, 1995). The economic impact of anthelmintic resistance is further complicated by the fact that, provided nutrition is good, healthy and productive sheep can be maintained on a farm with a minimum anthelmintic efficacy of 80%, although this figure is not sustainable, as the resistant nematodes will make ever more significant contributions to following generations (Barnes et al., 1995). To-date, there is no evidence to show that anthelmintic resistant nematodes are any more pathogenic than non-resistant nematodes, so resistance by itself is not production-limiting. Additionally, while anthelmintic resistance complicates effective nematode parasite control, in most cases, gastrointestinal nematodes can still be adequately managed.

Practical inefficacy of an anthelmintic drug group, due to resistance in nematode parasites might arise on a sheep farm in one or more of three ways: (i) by gene flow in nematodes introduced with newly arrived animals, (ii) following repeated exposure of nematodes to sub-therapeutic drug concentrations or (iii) by selection of pre-existing resistant nematodes by affording them a competitive advantage over susceptible nematodes (Prichard et al., 1980). Once resistance alleles have emerged, then effective exposure of nematode populations within their sheep host to anthelmintic drugs kills most of the susceptible nematodes and confers a selective advantage to those nematodes having resistance alleles. Faeces produced by the sheep or cattle host during the subsequent pre-patent period contain mostly eggs of the surviving resistant nematodes, which consequently contribute to a
greater proportion of succeeding generations. The evolution of resistance is thus determined by the extent to which survivors of the drug treatment contribute their genes to future generations. The rate of selection for resistance is, therefore, dependent on the number of genes involved, the dominance, partial dominance or recessiveness of the alleles and on the intensity of the selection pressure. The intensity of the selection pressure is influenced by the frequency and timing of anthelmintic treatments and by the drug efficacy, which is, in turn, influenced by the dose rate, its inherent efficacy and the pharmacodynamics and pharmacokinetics within the host. The rate of selection for anthelmintic resistance is also influenced by the life expectancy and fecundity of adult nematodes, the parasite generation interval, the ability or otherwise for the parasite to self-fertilise and the proportion of the susceptible population exposed to the anthelmintic compared with that on pasture (Martin, 1987). The frequency of alleles in a nematode population conferring anthelmintic resistance may also change due to the introduction of alleles conferring resistance or susceptibility with introduced animals. The impact of this would depend on the number of animals introducing resistance, the fecundity of the resistant nematodes and the subsequent management of these animals.

6. Strategies which may reduce the rate of development of anthelmintic resistance

There is a clear need for all sheep farmers to establish effective nematode control programmes that ensure satisfactory animal production, while preserving the efficacy of those anthelmintic drug groups that remain effective. The benefits of treatment of introduced animals with an anthelmintic drug or drug combination that is likely to be effective against resistant nematodes are obvious (West and Probert, 1989; Coles and Roush, 1992). However, the likelihood should be considered that alleles conferring anthelmintic resistance are already present in all flocks (Sargison et al., 2004), albeit at a low and clinically insignificant level in most. It is therefore important to ensure that these resistant alleles are not afforded any survival advantage as a result of nematode control practices. In practical managemental terms, the selection pressure for anthelmintic resistance is influenced by: the frequency and timing of anthelmintic treatment, the anthelmintic dose rate (Besier and Hopkins, 1988; Martin, 1989; Waller et al., 1996), the anthelmintic drug efficacy (Hennessy, 1993; Hennessy et al., 1994; Sargison et al., 1998) and the proportion of the susceptible population exposed to the anthelmintic compared with that on pasture (Michel, 1985; Van Wyk, 2001). Strategies aimed at reducing the rate of selection for anthelmintic resistance have been widely publicised and are based on these principles (Sargison, 2011).

7. The future of anthelmintic drugs

Parasitic nematodes have evolved to be highly complex organisms with life cycles that require the development and survival of free living stages in a variety of potentially adverse habitats and of parasitic stages within the hostile environment provided by their host. These characteristics are conferred by large genomes and a high level of genetic polymorphism (the model sheep parasitic nematode, H. contortus has a 2n = 11 (male) or 12 (female) karyotype and a genome that is now estimated to be about 300 Mb, possibly with up to 20,000 genes), which have enabled them to adapt to whatever evolutionary opportunities and challenges have been presented over a period of hundreds of millions of years. It would therefore be naïve to expect parasitic nematodes not to evolve complex mechanisms, in order to overcome the effects of exposure to pharmaceutical treatments aimed at their eradication or suppression. Therefore, control strategies, including those involving anthelmintic drugs, must focus on maintaining adequate productivity in the presence of nematode parasitism.

The five broad-spectrum anthelmintic drug groups have been developed through the random screening of synthetic or fermentative chemicals, such as botanical and industrial compounds (Geary et al., 2004). This process is both slow and expensive and it should be considered to be unlikely that any new class of anthelmintic drug for use in production animals will reach the market within the foreseeable future. The launch of the amino-acetonitrile derivative and spiroidole anthelmintic groups might help to reduce the impact of anthelmintic resistance in the short term, but also highlights the challenge of how to use anthelmintic drugs responsibly in order to maintain the practical efficacy of both new and existing drugs. Unfortunately, the molecular and population genetic basis of anthelmintic resistance is poorly understood, so the best advice that must be followed concerning its management is largely empirical. Scientific research needs to focus on understanding of mechanisms of anthelmintic drug action and on the molecular and genomic basis of resistance (Gilleard, 2006; Gilleard and Beech, 2007).

Full dose combinations of two or more anthelmintic drug groups with different modes of action have been shown to be effective in some cases against parasitic nematode populations that have developed resistance to single active anthelmintics, thus extending the useful life of each anthelmintic group (McKenna, 1990; Anderson et al., 1991). While resistance to combinations of two different anthelmintic drug groups has been reported (Bartley et al., 2004; Wagorn et al., 2006; Sargison et al., 2010), it has been proposed that the different active substances might each protect the other, thereby somehow slowing the development of resistance to the individual drugs (Anderson et al., 1988; Barnes et al., 1995; Dobson et al., 2001; Leathwick et al., 2009). However, the rationale for this approach to slow the emergence of resistance is dependent on the mechanisms of resistance to the different anthelmintic drug groups being under independent genetic control, thereby conferring additive efficacy when used in combination. Should shared or complex multiple mechanisms of resistance exist, for example involving P-glycoproteins involved with trans-membrane drug efflux pumps, or cytochrome p450 involved with drug metabolism (Blackhall et al., 2008; Mottier et al., 2008), then the rationale for the use of
combinations of different anthelmintic drugs would be less clear.

8. Concluding remarks

Control of parasitic gastroenteritis in intensively managed sheep flocks will always rely on the strategic use of anthelmintic drugs and selection for anthelmintic resistance is inevitable; hence, anthelmintic drugs need to be used alongside alternative control strategies, while ensuring that the rate of selection for resistance is minimised. Good nutrition and general disease management are prerequisites for effective nematode parasite control (Coop and Kyriazakis, 1999). However, currently unknown alternative strategies, such as genetic selection for both host resistance and reduced susceptibility to nematode parasites (Bisset et al., 1991; McEwan et al., 1997; Gray, 1997), the development of antiparasitic vaccines (Munn, 1993; Smith, 1993; Emery, 1996, Smith, 2006), manipulation of protein nutrition, grazing of bioactive forage crops (Niezen, 1995; Waller and Thamsborg, 2004) or the use of nematophagous fungi (Waller and Faedo, 1993; Grønvold et al., 1996) may prove to be useful and important adjuncts to control of gastrointestinal parasitism which could potentially reduce reliance on anthelmintic prophylaxis.

Conflict of interest statement

The author reports no conflicts of interest regarding the information provided in this manuscript.

References


