Anthelmintic resistance in sheep in Europe: A selected review

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ABSTRACT

Intensive use of anthelmintics to control gastrointestinal nematodes selects for anthelmintic resistance, which has become an important issue in many European countries. Presence of nematode strains resistant to benzimidazoles, imidazothiazoles and/or macrocyclic lactones has been repeatedly reported, particularly for the three most important genera, Haemonchus, Teladorsagia and Trichostrongylus. Additionally, multiple drug-resistant populations of these parasites have also been detected. Examples are given for the situation in European countries with differing climatic conditions and management systems of small ruminants. The widespread emergence of multi-resistant nematodes proves that the past intensive suppressive chemical control strategies may not be a successful approach any longer. Experience from the up to now development of anthelmintic resistance suggests that modern control schemes should not rely on sole use of anthelmintics, but employ other, more complex and sustainable recipes, combing chemical, environmental and immunological control.

1. Introduction

Gastrointestinal parasitism of small ruminants leads to tissue development and concomitant reductions in milk, wool and meat production, as well as reproductive performance. Gastrointestinal parasitism also causes morbidity, in certain cases mortality, while subclinical infections reduce significantly the overall income of sheep farmers (Jackson et al., 2009; Mavrogiani et al., 2011). Intensive use of anthelmintics to control gastrointestinal nematodes selects for anthelmintic resistance, which has become an important issue in most sheep-rearing countries, due to its clinical and financial significance (von Samson-Himmelstjerna, 2006; Cudekova et al., 2010).

2. Situation regarding anthelmintic drugs

In most European countries, the recent reports of anthelmintic resistance mainly refer to cases of benzimidazole- or levamisole-resistance and with increasing numbers of cases of resistance to macrocyclic lactones, particularly for ivermectin (Papadopoulos, 2008). Less commonly, reports exist for doramectin, which was found to be not effective (15% efficacy) in The Netherlands (Borgsteede et al., 2007), and moxidectin (44% efficacy), which was not to be found effective in Switzerland and Southern Germany (Scheuerle et al., 2009). Resistance against triclabendazole, the most widely used flukicide, has been also reported (Moll et al., 2000; Alvarez-Sanchez et al., 2006; Mooney et al., 2009). However, the problem appears to be reaching increased levels with the development of multi-drug resistant isolates (Sargison et al., 2007; Taylor et al., 2009). It is important to maintain the efficacy of currently available anthelmintics, wherever resistance has not developed and to prevent further selection of resistance where it has already started to become apparent (von Samson-Himmelstjerna, 2006). The new compound, monepantel, acts in a novel way compared to the already existing groups of anthelmintics against several nematode species (Kaminsky et al., 2009), hence it is of major importance to maintain its efficacy through strategic use and

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in conjunction with other effective drugs (Jackson et al., 2009).

3. Situation regarding anthelmintic resistance in sheep farms in Europe

The presence of anthelmintic resistance of sheep-derived nematodes has become a very common issue. Several studies exist in the international literature reporting prevalence of anthelmintic resistance from most parts in Europe, despite this becoming more difficult, and maybe also less interesting, in many cases and particularly for benzimidazole resistance, to publish any longer such reports in international scientific journals. Anthelmintic resistance in the field is usually noticed when helminth control policies fail dramatically; however, many cases remain without confirmation.

The prevalence rates differ significantly through the different areas, from north to south and west to east of Europe. On the other hand, it is becoming common to detect many species of nematode parasites showing resistance, even though the most common resistant genera are still Teladorsagia, Haemonchus and Trichostrongylus.

Some examples regarding presence of sheep anthelmintic resistance strains in different parts of Europe are presented here below.

In the United Kingdom, Taylor et al. (2009) found that 97% of sheep farms included in the study had populations containing alleles conferring resistance to benzimidazoles; a much lower frequency of resistance alleles to imidazothiazoles was found in the same study, with a lower prevalence (40%) of resistance on farms; moxidectin resistance was suspected in one case, since administration of the drug failed to remove completely triple resistant helminth populations. In all farms, Teladorsagia spp. was the predominant genus; multiple anthelmintic resistance was also detected in one or more genera, but most commonly in Teladorsagia spp., which, in two farms, was found to be resistant in three classes of anthelmintics. Similar multi-drug-resistant isolates have also been reported in several other parts of the United Kingdom (Bartley et al., 2004; Sargison et al., 2005, 2007).

In the Slovak Republic, resistance to abendazole was found in 4% and to ivermectin in 23% of the farms tested (Cernaska et al., 2006). On the contrary to the above relatively high prevalence of anthelmintic resistance cases, in Sweden it still remains low (5%) and restricted only to H. contortus and to the benzimidazoles (Hoglund et al., 2009). Resistance to benzimidazoles and ivermectin was found to be present in sheep farms in The Netherlands (Borgsteede et al., 1997, 2010).

In the para-Mediterranean countries, anthelmintic resistance is present, but has not reached, at the moment, a critical level. In Spain, presence of flock resistance, under field conditions, to benimidazoles varied from 18 to 35% and to macrocyclic lactones from 3 to 16%. In all cases, Teladorsagia spp. and Trichostrongylus spp. were the main genera involved (Alvarez-Sanchez et al., 2006; Diez-Banos et al., 2008). In Italy, levamisole resistance was found in all the farms and ivermectin resistance in two out of the three farms examined, suggesting a potential problem to sheep industry (Traversa et al., 2007). In France, Trichostrongylus axei has been reported to be benzimidazole-resistant in two flocks. Acquisition of resistance by helminthes infecting many animal species is important, as it facilitates spread of these resistant strains to other animal hosts, including those receiving infrequent anthelmintic treatments (Palcy et al., 2010). Furthermore, the same authors reported that resistant T. axei nematodes were found even 7 years after the anthelmintic selection pressure has been removed. In Greece, Teladorsagia spp. remains the dominant nematode infecting small ruminants and over 16% strains studied were found to be benzimidazole-resistant strains (Papadopoulos et al., 2001). Furthermore, Gallidis et al. (2011) reported the presence of 100% homozygous nezimidazole-resistant strains of H. contortus in dairy sheep flocks by using the allele specific-PCR method.

4. Situation regarding anthelmintic-resistant parasite genera

The presence of anthelmintic resistant nematodes has been repeatedly reported, particularly for the three most important genera of sheep nematodes, Teladorsagia, Haemonchus and Trichostrongylus. In a smaller proportion, as Cooperation and Nemafoxerus, were found resistant to anthelmintics. There are many reports for resistant strains available in the literature and, therefore, only some examples from some parts of Europe with different climatic and management systems will be presented.

In the United Kingdom, the predominant resistant species is Teladorsagia circumcincta, with strains found to be resistant to benzimidazoles, levamisole (Bartley et al., 2004) and the macrocyclic lactones (Sargison et al., 2001). Furthermore, multi-drug resistant isolates of this parasite have been reported from several parts of the UK (Bartley et al., 2004; Sargison et al., 2005). Additionally, Trichostrongylus spp. has also been reported to be ivermectin-resistant (Bartley et al., 2006). In Italy, levamisole and ivermectin resistant Teladorsagia and Trichostrongylus strains were detected in sheep farms (Traversa et al., 2007). In Spain, Teladorsagia spp. and Trichostrongylus spp. were found to be resistant to benzimidazoles, by using both in vivo and in vitro techniques, whilst only Teladorsagia spp. was found to be resistant to macrocyclic lactones (Alvarez-Sanchez et al., 2006). In Greece, Teladorsagia spp. is the dominant nematode and along with H. contortus, the two benzimidazole-resistant parasites present in the country (Papadopoulos et al., 2001; Gallidis et al., 2009, 2011). In Sweden, H. contortus was found to be benzimidazole and ivermectin-resistant (Hoglund et al., 2009). Other genera, such as T. axei, have been reported in central France to be benzimidazole-resistant (Palcy et al., 2010). H. contortus was the predominant resistant species against benzimidazole and moxidectin in Switzerland and Southern Germany (Scheuerle et al., 2009). Finally, on top to Teladorsagia spp. and H. contortus, which have been shown to be benzimidazole- and ivermectin-resistant, as in many other countries, resistant strains of C. curticei have been found in The Netherlands (Borgsteede et al., 1997, 2007, 2010).
Multiple drug resistant populations of *Teladorsagia*, *Haemonchus* and *Trichostrongylus*, the three economically most important species of nematodes infecting small ruminants, have been recorded in tropical, subtropical and in temperate regions of the world including Europe (Jackson et al., 2009).

5. Situation regarding diagnostic approaches towards anthelmintic resistance

Under field conditions, administration of anthelmintics continues to give clinical responses in parasitised animals, despite the apparent presence of resistant genotypes. Consequently, sheep farmers may remain unaware of any sub-optimal production performances and that the severity of resistance will increase rapidly if the anthelmintic remains in use (Taylor et al., 2009). If resistance in the field has reached the level of therapeutic failure, it is often too late to delay the onset and spread of resistance.

Palcy et al. (2010) concluded that the Faecal Egg Count Reduction Test (FECRT), a widely used method of assessing anthelmintic efficacy (Coles et al., 2006), has a low sensitivity for the detection of anthelmintic resistance in one nematode species in the context of multi-species nematode infections. They failed to detect resistance using the phenotypic measurement based on egg counts. However, post-mortem counts confirmed the presence of *T. axei* after benzimidazole treatment. Although it was possible that treatment suppressed egg production by the helminths, the most likely explanation is that the detection threshold of the technique was too low to detect faecal eggs. This finding illustrates the drawbacks of using FECRT to detect anthelmintic resistance in species, such as *T. axei*, which lay very few eggs. Hoglund et al. (2009) confirmed that FECRT is less sensitive than the molecular test for detecting benzimidazole-resistance, even though they suggested that both tests need to be interpreted carefully. It is clear, nowadays, that molecular methods can provide powerful tools to overcome many of the diagnostic disadvantages based on phenotypic characteristics.

The rapid development of molecular technologies has enabled considerable advances in the investigation of anthelmintic resistance. Genetic studies have shown that benzimidazole-resistance in trichostrongylid nematodes is mainly associated with the replacement of a phenylalanine (Phe, TTC) by a tyrosine (Tyr, TAC) at position 200 of the b-tubulin isotype 1 gene in *H. contortus*, *T. circumcincta* and *T. colubriformis*. Although less frequently occurring, the same single nucleotide polymorphism at position 167 has been observed in *H. contortus* and *T. circumcincta* and a rare polymorphism from Ala (GCA) to Glu (GAA) at position 198 of the b-tubulin isotype 1 gene has been detected in benzimidazole-resistant *H. contortus* (Elard and Hubert, 1999; Silvestre and Humbert, 2000). However, nematode genomes are full of different types of transposons and their potential involvement as potential mutator mechanisms in anthelmintic resistance has to be investigated (Gilleard, 2006).

6. Concluding remarks

The emergence of resistant helminths against the three broad-spectrum anthelmintic drugs is widespread in many parts of Europe. Furthermore, several multidrug resistant strains exist. It has been proved that the past intensive suppressive chemical control strategies may not be a successful approach any longer. The control schemes relying on the sole use of anthelmintics need to be replaced with other more complex and sustainable ones, combining chemical, environmental and immunological controls (Bath, 2011). New philosophy and approaches, such as the targeted selective treatments, taking into account the nematode population in refugia, should be adopted (Kenyon et al., 2009). On the other hand, new compounds, such as monepantel, may be effectively used as quarantine drenches, using a single product instead of combinations, which were previously recommended for this purpose in order to reduce the risk of importing resistance into the flock. Additionally, any new compound and formulation should be included into sustainable parasite control strategies with care and not exclusively, but rather in conjunction with remaining effective products, in order to conserve susceptibility within parasite supra-populations (Jackson et al., 2009).

Conflict of interest statement

The authors report no conflicts of interest regarding the information provided in this manuscript.

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