Veterinary Parasitology 185 (2012) 9–15

Contents lists available at SciVerse ScienceDirect

Veterinary Parasitology

journal homepage: www.elsevier.com/locate/vetpar

Anthelmintic resistance in non-strongylid parasites of horses

Craig R. Reinemeyer*

East Tennessee Clinical Research, Inc., 80 Copper Ridge Farm Road, Rockwood, TN 37854, USA

ARTICLE INFO

Keywords:
Parasite control
Horses
Anthelmintic resistance

ABSTRACT

Since 2002, selected populations of *Parascaris equorum* in several countries have been reported to survive treatment with macrocyclic lactone (M/L) anthelmintics. Clinical treatment failures are characterized by negligible fecal egg count reduction, but M/L resistance has been confirmed in ascarids by controlled efficacy testing. Resistance was selected by current parasite control practices for foals, which often include exclusive and excessively frequent use of M/L dewormers, thereby minimizing *refugia* within the host and in the environment. Chemical control of M/L-resistant isolates can be accomplished with pyrimidine and/or benzimidazole anthelmintics, but a few M/L-resistant populations have recently exhibited resistance to pyrantel pamoate as well. Some specimens of *Oxyuris equi* regularly survive treatment with macrocyclic lactones, but it is uncertain whether this constitutes resistance or merely confirms the incomplete oxyuricidal efficacy of virtually all broad spectrum equine anthelmintics. Variations in other biological parameters of *Oxyuris* and *Parascaris*, specifically atypical infection of older hosts and shorter prepatent periods, have been reported anecdotally. These changes may represent genetic modifications that have evolved in parallel with resistance as a result of anthelmintic selection pressure.

1. Introduction

The parasites of equids that are routinely targeted by anthelmintic therapy include nematodes of the superfamilies Strongyloidea, Ascaroidea, Oxyuroidea, and Rhabditoidea, as well as cestodes of the family Anoplocephalidae. Anthelmintic resistance involving equid parasites was first described with phenothiazine in cyathostomin nematodes (Strongyloidea) over fifty years ago (Poynter and Hughes, 1958; Gibson, 1960; Drudge and Elam, 1961). In the ensuing five decades, the majority of cyathostomin populations in North American horses have developed resistance to benzimidazoles (Kaplan, 2004; Kaplan et al., 2004), nearly half can also survive treatment with pyrimidines (Kaplan, 2004; Kaplan et al., 2004; Brazik et al., 2006), and a few populations are resistant to piperazine (Drudge et al., 1983). The first reports of anthelmintic resistance involving a second superfamily of nematodes (Ascaroidea) in horses appeared only recently (Boersema et al., 2002; Hearn and Peregrine, 2003).

Equids and their helminth parasites have likely coexisted for tens of thousands of years. Undoubtedly, the most drastic disturbance during the entire history of this evolutionary association has been the introduction of chemical parasiticides, especially when those with very high efficacy are used frequently and repeatedly. Anthelmintic resistance is the best-known manifestation of parasitic adaptation to overwhelming selection pressure, but undetected changes in other biological factors also may have evolved concurrently.

The objective of this paper is to review the current status of anthelmintic resistance among non-strongylid parasites of horses, and to discuss the biological factors and control practices which foster the development of resistance. General recommendations will be offered for managing certain equine parasitisms in the face of growing resistance. Hypothetical biologic changes that could seriously complicate effective equine parasite control will also be discussed.

* Tel.: +1 865 354 8420; fax: +1 865 354 8421.
E-mail address: crr@easttenncr.com

0304-4017/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetpar.2011.10.009

The majority of this presentation will address known and potential changes in *Parascaris equorum* and *Oxyuris equi*.

1.1. P. equorum

P. equorum (ascarid; roundworm) is a ubiquitous nematode parasite which occurs in the small intestine of juvenile horses world-wide.

1.1.1. Relevant biology

Ascarid eggs are passed in the feces of the host, and development to the infective stage requires about 10 days at temperatures of 25–35 °C (Clayton, 1986). The infective unit is an egg containing a second-stage larva (L_2); larvated eggs can survive on premises for five to 10 years. Infective eggs are ingested from the environment, hatch in the gut, and larvae subsequently migrate through the liver and lungs before returning to the small intestine as fourth stage larvae (L_4). Ascarids mature progressively in the gut and begin to lay eggs approximately 75–80 days after infection (Clayton, 1986).

Horses ultimately develop strong protective immunity against ascarids by one year of age, so infections are generally limited to juveniles. Patent infections are encountered infrequently in horses older than two years.

1.1.2. Anthelmintic resistance

Failures of macrocyclic lactone treatments to decrease *Parascaris* fecal egg counts were first reported in Boersema et al. (2002) and Hearn and Peregrine (2003). Subsequent reports indicate that macrocyclic lactone-resistant populations of *P. equorum* are widespread in several countries (Craig et al., 2007; Lyons et al., 2008a; Schougaard and Nielsen, 2007; Slocombe et al., 2007; Von Samson-Himmelstjerna et al., 2007; Veronesi et al., 2010).

Clinical evidence for macrocyclic lactone resistance (M/L-R) consists of apparent failures of ivermectin (IVM) or moxidectin (MOX) treatment to disrupt ascarid reproduction. Because fecal egg count reduction testing (FECRT) has not been validated for *Parascaris*, however, a formal efficacy study was performed in 2005. Eleven foals that had been raised helminth-free were inoculated orally at 6 weeks to 3 months of age with ~500 larvated eggs of a Canadian isolate of *P. equorum* that was purported to be resistant to macrocyclic lactone anthelmintics (Kaplan et al., 2006). Compared to untreated, control foals in this study, oral ivermectin paste (200 μg/kg) did not significantly reduce fecal egg counts for 13 days post-treatment, and only decreased worm numbers at necropsy by 22%. This study provided unequivocal confirmation that the Canadian *Parascaris* isolate was resistant to ivermectin. A subsequent study with small numbers of foals further demonstrated that populations of this isolate were unaffected by alternating treatments of ivermectin and moxidectin, indicating that resistance involved the entire macrocyclic lactone class, and not just single entities of this chemical family (Reinemeyer and Marchiondo, 2007).

1.1.3. Biological factors promoting resistance

All broad spectrum anthelmintics have an Achilles' heel, often designated as a dose-limiting parasite (DLP). Among the target parasite species and stages listed on a product's label, one (the DLP) always requires a higher dosage of the active agent than all the rest to achieve a label claim for efficacy (Anonymous, 2001). The majority of currently marketed equine anthelmintics are considered "broad spectrum", which indicates that they have acceptable efficacy (>90%) against four different target parasites: large strongyles, cyathostomins, ascarids, and pinworms. *Parascaris* is the DLP for all current, broad-spectrum, equine anthelmintics except pyrantel pamoate.

Fenbendazole (FBZ) provides a ready example of *Parascaris*' role as a dose-limiting parasite. In adult horses, the 5 mg/kg dosage of FBZ (Panacur®, Intervet Inc., Millsboro, DE 19966) has label claims for acceptable efficacy against large strongyles, cyathostomins, and pinworms. The recommended dosage of FBZ for removal of *Parascaris*, however, is 10 mg/kg.

Relevant to the present discussion, all DLPs have a lower threshold for the potential development of resistance because the difference between the effective dosage and the label dosage is smaller for DLPs than for other target organisms.

1.1.4. Pharmacologic factors promoting resistance

Macrocyclic lactones maintain prolonged, effective plasma levels, and comprise the most persistent class of anthelmintics currently approved for use in horses. An undesirable feature of persistent pharmacokinetics, however, may be protracted exposure of target parasites to subtherapeutic drug concentrations, which can select for anthelmintic resistance (so-called "tail selection"; Sangster, 1999). Persistent anthelmintics minimize *refugia* within the host, especially for target species with long prepatent periods.

1.1.5. Contemporary control practices

At many breeding farms, it is common practice to treat foals with ivermectin before one month of age, presumably for management of *Strongyloides* infection. Thereafter, various anthelmintics are administered in rotation at monthly intervals for the first year of life to control ascarids and other potential parasites of juvenile horses. Many farms use a macrocyclic lactone in this rotation at least bimonthly (Craig et al., 2007). (*Note*: *Moxidectin* [Quest Gel, Fort Dodge Animal Health, Fort Dodge, IA 50501] *is not labeled in the United States for use in foals less than six months of age.*) Because macrocyclic lactones are larvicidal against *Parascaris*, every dose administered to a foal theoretically minimizes *refugia* within the host at that time. Further, if M/Ls consistently recur in the rotation at intervals less than the prepatent period of *P. equorum*, every single ascarid acquired by the foals on that premise would be exposed to M/L treatment at some point prior to reaching maturity. Finally, repeating treatments at intervals less than the prepatent period or egg reappearance period effectively denies susceptible genotypes an opportunity to reproduce, and thus serves to minimize *refugia* in the environment. Such practices feature exclusive and/or excessively frequent use of a single drug class, which is known to select very intensively for the development of anthelmintic resistance (Kaplan, 2004).