Using coccidiostats: trends and alternatives

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INTRODUCTION

It is possible to produce broilers, efficiently, without the help of antimicrobials; the key for success is not only to ensure an adequate animal performance, but to prevent economical losses that may be difficult to recognize until it is too late. Factors such as coccidiosis (Al-Sheikh and Al-Saieg, 1979; Jackson *et al.*, 2003), high dietary levels of protein (Kocher *et al.*, 2003; Palliyeguru et al., 2010), high animal densities, stress and immunosuppression (Lee *et al.*, 2011) are involved in the pathogenesis of necrotic enteritis (NE), one of the most commonly diagnosed diseases in poultry industry. Necrotic enteritis is a complex process where the gastrointestinal epithelium morphology is affected by protozoa and bacteria (as *C. perfringens*), reducing villi length, slowing down its regeneration, and in the most extreme affection, necrotizing the intestine, with a fatal outcome for the animal

Future restrictions on the use of coccidiostats increase the incidence and severity of NE on farms (Elwinger *et al.*, 1992), which in its subclinical affection may be a major cause of economic losses in poultry production (Dahiya, 2006)

COCCIDIOSIS CONTROL: RESISTANCE DEVELOPMENT

The widespread use of chemical compounds for the control of avian coccidiosis has developed drug resistance in *Eimeria*. Resistance is usually one of the major failures recognized in the parasite control, but the formal definition is a reduction in the sensitivity of a parasite in front of a specific drug (Sangster and Dobson, 2001). The World Health Organization Scientific Group (1965), developed the definition of resistance in its broadest sense as "the ability of a parasite strain to survive and / or multiply, despite the administration and absorption of a drug at equal or greater dose, than usually recommended within the tolerance limit of the subject". There are many types of resistance: a) acquired: heritable reduction of the sensitivity of certain *Eimeria* strains to drugs along the time; b) cross-resistance: resistance interchange between different compounds with a similar mode of action; c) multiple: resistance to more than one drug despite having different modes of action. To understand the enrolled mechanism in developing drug resistance of *Eimeria* isolates, it is necessary to know and understand the modes of action of anticoccidial drugs. There are different modes of action of these drugs (Abba *et al.*, 2011; Table 1), for instance, effects depending on the membrane (ionophore), energy metabolism (quinolones, clopidol, nicarbazin and robenidine), co-factor synthesis (amprolium, sulfonamides) and DNA synthesis (arprinocide)

Anticoccidial drugs	Mechanism of action	Species studied	References
Halofuginone	Unknown	Several species	Kitandu *et al.*, 2006
Toltrazuril	Acts in front genome	Several species	Hackstein *et al.*, 1995
Benzeneamines	Uncoupling oxidative phosphorylation	Several species	Bafundo *et al.*, 1989
Diclazuril	Nucleotide analogs	*E. tenella*	Maes *et al.*, 1988
Ionophores	Cation transport across membrane	Several species	Smith and Galloway, 1983
Monensine	Influx of sodium ions	*E. tenella*	Smith and Galloway, 1983
Clopidol	Affects to electron transport	*E. tenella*	Fry and Williams, 1984
Robenidine	Link to the protein and cause the uncoupling of mitochondria parasite	Several species	Wang, 1982
Amprolium	Thiamine antagonist	*E. tenella*	James, 1980
Sulphonamides	Inhibition of folic acid pathway	*E. tenella*	Wang *et al.*, 1975
Decoquinate	*Inhibits respiration by blocking*	*E. tenella*	Wang, 1975

Table 1. Anticoccidial drugs and their mechanisms of action

RESISTANCE MANAGEMENT

Multiplication control and spread of resistant strains of *Eimeria*

In order to control multiplication and spread of isolated strains from *Eimeria* there are general recommendations for the control of coccidiosis. Under conditions of intensive rearing, coccidia oocysts are ubiquitous and spread easily having a huge potential of reproduction in poultry farms. In the floor, sporulation of the oocysts is very fast, especially in the presence of 60-80% of moisture. Although sporulated oocysts start to decrease in number after three weeks in the presence of bacteria, other organisms and ammonia (Williams, 1995), several steps are needed to reduce the exposure of birds to them. It is recommended to change litter next to drinkers and apply a dry coat before entering new chicks. It is also useful to improve the drinkers and ventilation in order to inhibit sporulation (Ruff, 1999). The main factors to be considered in the environmental management are good ventilation, cleaning between flocks, eliminating sources of moisture and keeping dry litter, optimum density of animals, less stress and good management of feed and water. Another good way that allows the destruction of oocysts is to practice all in – all out between flocks. In addition, an important role is the biocontrol measures in order to minimize the spread of resistant oocysts. In the case of breeding chickens, biosecurity measures are particularly necessary (Allen and Fetterer, 2002)

Introduction of rotation programs

The rotation of coccidiostats in poultry industry has been one of the tools to combat the development of *Eimeria*'s resistance to multiple drugs (Daugschies *et al.*, 1998). In these programs, two or more drugs belonging to different classes of coccidiostats are used in the same flock, for example, use of one type of drug in starter diets, another in the growing period and finally, at the start of the finishing period followed by a wash-out at the end

Use of alternatives

The two major tools to control coccidiosis are to improve immunity and to reduce oocysts intake. Vaccination is another valid method. In the field, it has obtained good results in the application of anticoccidial drugs combined with vaccines. A typical program is the use of a drug (or program) on several flocks followed by vaccination in the incomming flocks and then return to the initial drug (Chapman, 2000). Live vaccines provide help diluting resistant genotypes present in sheds with susceptible genotypes from isolated vaccines. Therefore, the *Eimeria* control with non-drug means a dilution of resistant genes. These drugs may include non-botanical anticoccidial vaccine to control coccidiosis. The use of botanical anticoccidiostats and other natural products can provide a novel approach for controlling coccidiosis, an urgent necessity of control due to increasing drug resistance by the parasite strains occurring in poultry production (Allen and Fetter, 2002). Natural dietary supplements in animals improve their innate defense mechanisms, eliminating or reducing the need for therapy for these enteric infections, in an effectively way (Alfaro *et al.*, 2007). A large number of plant-derived compounds (Alfaro *et al.*, 2007, Naido *et al.*, 2008, Abbas *et al.*, 2010) and natural products (Allen and Fetterer, 2002) seem to have anticoccidial activity against *Eimeria* species commonly found in poultry. However, these bio-active products should be tested to establish its anti-parasitic activity

Fighting the cause

If protozoa and bacteria are damaging the intestinal epithelium in this disease, it seems wise to try to reduce the contact of the animal with those microorganisms, whilst at the same time, enforces the gastrointestinal tract epithelium renewal

A combination of sodium butyrate with essential oils (NT) protected with vegetable fat improved growth performance and reduced the incidence of necrotic enteritis (Jerzsele *et al.*, 2012) in the absence of coccidiostats in challenged animals. In this test NT supplementation showed significant increase in body weight of chickens, increased the length and Villus: Crypt ratio (Table 2) and decreased the score of pathological and histopathological lesions compared to the control (Figure 1). It also demonstrated significant differences in pathologic lesions ($P < 0.05$) versus the group receiving essential oils only. This combination (NT) promotes renewal of intestinal epithelium and controls the microflora. The explanation for the synergistic action, between sodium butyrate and essential oils, may be that the first improves epithelial regeneration and the second decreases the amount of alpha-toxigenic *Clostridium* that can adhere to the surface and produce the toxin that finally causes NE

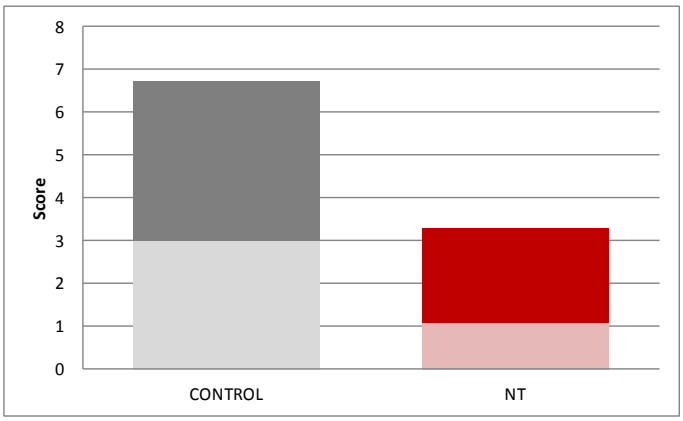

Figure 1. Macroscopic and microscopic changes (score) in broilers with necrotic enteritis by adding NT (combination of sodium butyrate and essential oils protected with vegetable fat)

Group	Villus lenght (µm; average ± SEM)	V:C Ratio (average ± SEM)
Control	844.8 ± 39.35	5.23 ± 0.26
NT	1028.9 ± 24.81**	5.73 ± 0.25*

*** P<0.05; ** P<0.001 statistical differences compared to the control**

Table 2. Average of villus lenght and Villus:Crypt ratio (V:C) in broilers with necrotic enteritis fed with a standard diet (Control) or treatment diet (NT; combination of sodium butyrate and essential oils protected with vegetal fat)

The following evidence presented at the World's Poultry Science Journal (Mallo, 2012) was conducted in order to assess whether the combination was effective against coccidiosis in vaccinated broilers. A total of 528 Ross broilers 308 of 1-day old were randomly allotted in two experimental treatments: control (T1) and NT vaccinated against coccidiosis at 3 days of age (T2). Each treatment was replicated 12 times with 22 male broilers each. The basal diets of each period (starter and finisher) were formulated to be isonutritious. Oocysts excretion in feces was lower after supplementation with sodium butyrate and essential oils combination, protected with vegetable fat (Figure 2). A reduction of oocysts in litters was also observed with NT at 21 days of age (66.9%; 44 vs 133 oocysts / g litter; NS) and no oocysts were found in litterin litter at 35 days with NT (0 vs 22 oocysts / g litter; P = 0.12)

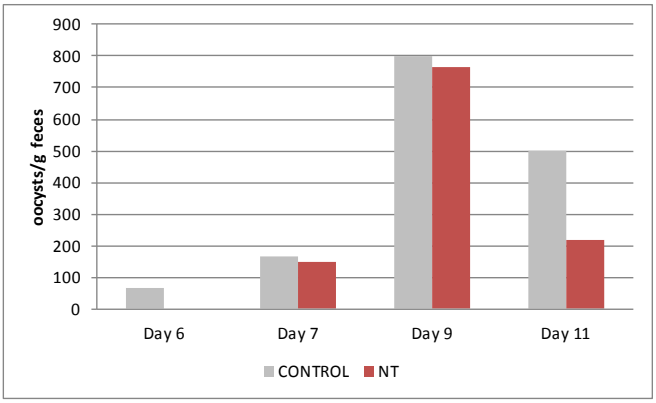

Figure 2. Reduction in oocyst excretion by adding NT in broiler diets

In a field evaluation (Puyalto, 2016) one thousand 1-day old pullets were distributed in two treatments: control treatment (C) and experimental treatment (NT), control diet with protected sodium butyrate and essential oils, added on top at 1kg/t in starter feed (1-5 weeks) and at 0.5 Kg/t in grower feed (6-16 weeks). The average body weight was 43 g higher at the end of the trial for NT group (1.175 Kg vs 1.132 Kg). Feed intake was equal for both treatments (4.2 Kg). Flock uniformity of group with butyrate and essential oils in protected form was 98% versus a 78% in the control group (Figure 3). Regarding health condition, animals in treatment C showed signs of necrotic enteritis, emaciation and respiratory diseases but these signs were not shown in NT group. Feathers remained white in NT group and dirty in C group. There were differences in mortality as well, C group had a 4.5% of mortality at the end of the trial, whilst NT group had less mortality, 3.5%

It can be concluded that the use of sodium butyrate and essential oils in protected form on pullet feed, allows higher growth, better FCR, flock uniformity and health status

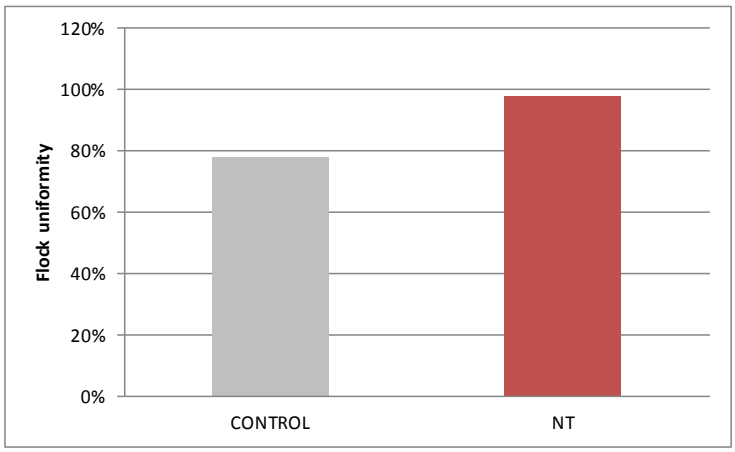

Figure 3. Increase in flock uniformity by adding NT in the pullet diets

CONCLUSION

Sporadic outbreaks of necrotic enteritis are one of the most important threats to the poultry industry. These increased significantly in Europe after the ban on subtherapeutic antibiotics. The use of coccidiostats is possibly one of the main tools used in the control of the disease. However, due to the resistances and future restrictions in the use of anticoccidiostats it is necessary to study and establish other strategies of control. As tactical measures for the control of coccidiosis, it should be useful the use of vaccines in combination with synthetic and botanical anticoccidials, together with a proper education of farmers about practices for the control of this parasite. Future research should be focused on evaluating the integration of these measures