Prospects for the Extended Use of Maxiban® as an Anticoccidial for Broiler Chickens

THOMAS K. JEFFERS, Ph.D., Courtesy Professor

Department of Animal Science, Cornell University

Ithaca, New York USA

Summary

United States as well as European poultry producers currently have four options for coccidiosis control: full ionophore programs, the use of chemical anticoccidials, coccidial vaccines, and the long-term use of Maxiban. Producers using Maxiban in the starter and grower have experienced consistently effective anticoccidial action, resulting in growth performance. With widespread and growing use of Maxiban in the starter and grower, producers and veterinarians have expressed concern that extended use will create Maxiban-resistant strains of coccidia. Field and laboratory research, however, suggest that such concerns are unwarranted.

Introduction

Maxiban is a premix containing equal proportions of narasin and nicarbazin approved for use as an anticoccidial at final feed concentrations of 54 to 90 grams/ton (60 to 100 ppm). This is a patented anticoccidial based upon the synergistic activity of nicarbazin in combination with all polyether ionophores (Callender and Jeffers, 1980).

There are two general classes of anticoccidial drugs currently available for use in broilers. The ionophores, examples being monensin, narasin and salinomycin, and the "chemical" anticoccidials, examples being halofuginone, robenidine and diclazuril. Maxiban is in a class by itself and may be described as a potentiated chemical.

The unique mode of anticoccidial action of the ionophores is due to an alteration of cation gradients following direct uptake of the drug by extracellular invasive stages of coccidia. This results in lethal ionic imbalances in the invasive stages of the coccidian parasite, killing the coccidia shortly after their invasion of epithelial cells in the chicken's intestine, well before any intestinal damage can occur (Smith and Galloway, 1983; Smith and Strout, 1979; Smith et al., 1981).

Maxiban was found to be highly effective against a wide array of field isolates of coccidia in both battery cage and floor pen trials conducted in the United States and Europe (Callender, et al. 1987a, 1987b; Tonkinson, et al., 1987).

It is thought that the synergistic activity (1:1 mixture of narasin [ionophore] and nicarbazin [chemical]) of Maxiban results from the expression of anticoccidial activity beyond that of narasin or nicarbazin alone, affecting all asexual stages of coccidial development.

Many poultry producers have found that they obtain consistently effective anticoccidial control–and in turn, outstanding growth performance–while using Maxiban in both the starter and grower diets. However, some have expressed concerns about the continuous use of Maxiban, fearing that resistance will develop and Maxiban would then not be as useful in their poultry rations. Such fears are unwarranted based upon the available scientific information.

Key Points

- Ionophores such as monensin, salinomycin and narasin destroy coccidia by creating lethal ionic imbalances within the coccidian cell structure during extracellular invasion.
- Maxiban combines an ionophore–narasin–with nicarbazin to create a highly effective synergistic effect that acts against every asexual phase of the coccidian life cycle.

Drug Resistance: Definition and Development

There is no universally accepted definition of anticoccidial drug resistance. Different investigators use different drug testing procedures, quantify the response of coccidia to anticoccidial drugs in different ways, and use different end-points in drug activity to distinguish between drug resistance and sensitivity, making it virtually impossible to precisely define anticoccidial drug resistance.

Resistance may best be expressed in relative terms ranging from reduced drug sensitivity (a situation in which increased anticoccidial dosages within an approved dosage range may offer more complete anticoccidial efficacy), to "classical" drug resistance (a situation in which the respective anticoccidial drug provides essentially no anticoccidial efficacy, even at the highest approved drug dosage) (Jeffers, 1989).

The presence of numerous coccidia in virtually every poultry facility provides a large reservoir of genetic variation from which drug-resistant strains may be selected. Anticoccidial drug resistance results from an increase in the frequency of genes determining this trait in the coccidial population (an increase in the gene frequency or in the incidence of organisms with genes expressing this trait). Therefore the magnitude of the change in resistance is proportional to the magnitude of changes in gene frequency (Jeffers, 1978; Jeffers and Shirley, 1982). Anticoccidial drugs provide the basis for changing gene frequency through genetic selection, which in this context may be defined as allowing some kinds of coccidia to reproduce more effectively based on their relative sensitivity to the anticoccidial drug to which they are exposed. Furthermore, the nature of the coccidian life cycle favors the efficient selection of resistant coccidia from a genetically variable population because, during the majority of their life cycle, coccidia are undergoing asexual division and are in a haploid chromosomal configuration. The principal activity of virtually all anticoccidial drugs is directed against these asexual haploid stages (i.e., sporozoites and merozoites) and can therefore very efficiently eliminate the more sensitive individuals in the population, allowing the more resistant individuals to multiply and increase in frequency within the population.

Key Points

- Anticoccidial drug resistance ranges from reduced sensitivity to "classical" drug resistance.
- Genetic diversity of coccidia within broiler flocks creates the possibility for development of resistance to anticoccidial drugs.
- The predominance of asexual stages in the coccidian life cycle speeds the development of resistance.

Resistance Development: Ionophores vs. Chemicals

Most of the attempts to experimentally develop strains of coccidia resistant to the ionophores in the laboratory have focused on monensin, probably because it has been available for use in different laboratories longer than any other ionophore. In any case, attempts to develop monensin-resistant strains of coccidia in the laboratory have been largely unsuccessful (Chapman, 1976; McLoughlin and Chute, 1974; Shumard and Callendar, 1969; Weppleman, et al., 1977). Likewise, attempts to intentionally develop resistance to the related polyether ionophores emericid, lasalocid and narasin, respectively, were unsuccessful (Benazet et al., 1976; Chapman, 1976; Jeffers, 1981; Mitrovic and Schildknecht, 1975).

The unique mode of action of the ionophores likely accounts for the difficulty that the coccidia have in developing resistance to them (Smith, 1981). Fundamental changes in the biophysical properties of the cell wall of the coccidia would be required in order to cope with the biochemically non-specific action resulting from the transmembrane cation transport activities of the ionophores. Such changes would likely require significant complex genetic changes, which are not easily accomplished even through intensive selection.

In view of the extensive use of the ionophores in commercial poultry production, more recent attention has been given to the drug sensitivity of field populations of coccidia, which have been exposed to ionophores far more extensively than was the case in any of the laboratory experiments. Several investigators have reported various degrees of resistance to the ionophores among field isolates of coccidia from several different countries (see review by Jeffers, 1989). Although these reports are variable, there are two points of similarity among them. Firstly, *Eimeria tenella*, the causative agent of cecal coccidiosis, was the species of coccidia most often reported to have exhibited a loss of sensitivity to the ionophores. Secondly, in none of these manuscripts was there a complete loss of the effectiveness of the respective ionophore against the field isolate of coccidia.

Unlike the ionophores, the chemical anticoccidials act at very specific points in biochemical pathways, usually the specific inhibition of an essential enzyme within the metabolic activities of the coccidia, some examples being the inhibition of folic acid biosynthesis by the sulphonamides; the inhibition of thiamine uptake by amprolium; the inhibition of mitochondrial respiration by the quinolones; and the inhibition of mitochondrial respiration using an alternative pathway by clopidol. Unlike the broader and less specific mode of action of ionophores, such specific effects of these chemical anticoccidials are relatively easy

for the coccidia to overcome through resistance development. Sometimes only a single gene mutation can lead to complete resistance to such highly specific modes of anticoccidial action. This is "classical" anticoccidial drug resistance, the characteristics of which are that resistant strains cannot be controlled by increasing drug concentrations and such resistance may therefore lead to widespread "coccidiosis breaks" within a poultry complex. Drug–resistant strains of coccidia have been intentionally developed in the laboratory to essentially all of the chemical anticoccidials that have been discovered during the past 50 years (for a review see Chapman, 1982).

Likewise, field isolates resistant to chemical anticoccidials have been readily isolated from field populations of coccidia in several different countries (Chapman, 1978, 2003; Jeffers, 1974a, 1974b; McDougald, 2003; McDougald et al., 1986, 1987, 1997; Ryley, 1980; Ryley and Betts, 1973).

The synergistic anticoccidial mode of action of Maxiban is likely to be even more complex than that of ionophores alone, thus requiring even more extensive genetic changes in the coccidia to circumvent making resistance development very unlikely (McDougald, 1982; Radostits, 1980; Smith, 1981).

In the most intensive and extensive attempt to intentionally develop anticoccidial drug resistance in the laboratory that has been reported to date, Bafundo and Jeffers (1990) were unable to develop resistance to an ionophore/nicarbazin combination. They attempted to develop resistance in *E. acervulina* and *E. tenella* through 60 generations of selection in an experiment designed to maximize selection pressure in each generation of selection. Although this extensive period of intensive selection resulted in some reduction of sensitivity in the selected strain of *E. acervulina* when compared to the parent strain from which it was derived, the *E. tenella* strain remained fully sensitive to the ionophore/nicarbazin combination.

Furthermore, to my knowledge, there have been no published reports of the development of resistance to Maxiban under field use conditions.

Key Points

- The more specific the mode of anticoccidial action, the more readily it is overcome by the genetic diversity of coccidian populations.
- Chemical anticoccidials—such as halofuginone and robenidine—employ a very specific mode of action that is readily overcome by coccidia, which results in "classical" resistance.
- The mode of action used by ionophores is highly generalized and would require complex genetic and biophysical changes for coccidia to overcome.
- *In vitro* attempts to develop ionophore-resistant coccidian strains have been unsuccessful.
- One species, *E. tenella* (the causative agent of cecal lesions in broiler chickens), has shown ability to develop reduced sensitivity to ionophores in field studies.
- In multi-generation lab studies, *E. tenella* was unable to develop resistance to Maxiban.

OPTIONS FOR CONTROL OF COCCIDIOSIS

Full Ionophore Programs

The ionophores remain the backbone of coccidiosis control programs worldwide because of their continuing effectiveness in preventing coccidiosis and their freedom from significant drug-resistance problems.

Chemical Programs

Chemical anticoccidial programs present a difficult continuing management challenge for the poultry producer because of the high likelihood that the coccidia may readily develop resistance to the chemical anticoccidial being incorporated in the anticoccidial program. Therefore, when using a chemical anticoccidial program, broiler coccidial lesions scores and flock performance must be closely monitored to assure that intestinal health and optimum growth performance are maintained. Rapid onset of resistance may require more frequent program changes. Such monitoring programs are costly and detract from attention that must be paid to managing other elements of the poultry production enterprise.

Furthermore, chemical anticoccidials have no known activity against *C. perfringens* and therefore offer no ancillary benefit in the control of necrotic enteritis.

Vaccines

Commercially available coccidia vaccines for broiler chickens in the U.S. all contain live oocysts of several species of chicken coccidia. These may be either fully pathogenic oocysts derived from wild-type strains of coccidia, or oocysts of attenuated strains produced through selection for precociousness.

Although coccidia vaccines have been used extensively in broiler breeders, use in broiler production has been much more limited. However, additional interest in the use of coccidia (vaccines) in broiler production has been prompted by the notion that the use of such vaccines will result in a restoration of anticoccidial drug sensitivity of the resident coccidial population, though there is scant valid scientific information to support this notion.

Perhaps the most challenging objective in the use of coccidia vaccines in broiler production is assuring uniformity in the growth performance of broilers following vaccination. This is due to the fact that coccidia vaccines, unlike bacterial or viral poultry vaccines, do not elicit protective immunity following the initial vaccination.

The first variable contributing to a lack of uniformity is the vaccination method itself, often being the use of a spray cabinet in the hatchery, in which chicks ingest variable numbers of oocysts in the random process of preening themselves.

A second very important variable is the requirement for repeated coccidial infections during the grow-out in order to obtain protective immunity. This is again a random process of ingestion of oocysts from the litter, resulting in coccidial infections of variable severity in the absence of an effective anticoccidial medication program, thus compromising intestinal health and the bird's growth performance. As genetic improvement continues to shorten the time it takes broilers to reach the desired market weight, obtaining protective immunity prior to slaughter becomes even more challenging.

Maxiban in the Starter and Grower Diets

The use of Maxiban in the starter and grower diets offers the opportunity to overcome all of the drawbacks for the other three options cited above. Maxiban has outstanding activity against *E. tenella* without the need for roxarsone in the ration and is therefore able to eliminate outbreaks of cecal coccidiosis during times of high challenge. Lastly, and perhaps most importantly, intensive attempts to develop *E. tenella* resistance to Maxiban in the laboratory were unsuccessful, and there have been no reports of resistance problems resulting from the use of Maxiban in the field (Bafundo, 1990). Thus the prospects for extended use of Maxiban in starter and grower diets without the threat of resistance problems are very positive. Clearly, among the four options considered for the prevention of coccidiosis, the use of Maxiban in the starter and grower diets is a very effective option.

Key Points

- *E. tenella* "leakage" is the one significant weakness of full ionophore programs.
- Chemical anticoccidial programs require intense management and flock monitoring, and often more frequent program changes due to the rapid development of resistance, taking valuable time away from other elements of the poultry operation.
- Coccidial vaccines present the possibility of introduction of clinical coccidiosis to the flock and inevitably compromise intestinal health.
- Maxiban helps intestinal health by providing anticoccidial effectiveness, with the added advantage of *E. tenella* control.

Conclusion

Laboratory and field data suggest that Maxiban used in both the starter and grower diets is a very effective coccidiosis prevention program and intestinal health option available to producers of broiler chickens. The lack of any field or laboratory evidence of resistance to Maxiban reinforces the positive prospects for long-term use of Maxiban in the starter and grower diets. Producers, nutritionists and veterinarians should consider this when planning for long-term prevention of coccidiosis.

Maxiban® directions for use:

- For coccidiosis prevention, feed Maxiban at **54-90 g/ton**
- Feed continuously as the sole ration
- Requires a 5-day withdrawal

CAUTION: Ingestion of narasin by adult turkeys, horses or other equine species has been fatal. Do not feed to laying hens.

The label contains complete use information, including cautions and warnings. Always read, understand and follow the label and use directions.

References:

Bafundo, K.W. and T.K. Jeffers. 1990. Selection for resistance to monensin, nicarbazin, and monensin plus nicarbazin. *Poult. Sci.* 69: 1485-1490.

Benazet, F., Cartier, J.R., Flourent, J., Johnson, C., Lunel, L., and D. Mancy. 1976. Eimericid (31, 559 R.P.): A new anticoccidial. *Proc. 9th Int. Congr. Chemotherapy* 6: 91-96.

Brennan, J., Bagg, R. Barnum, D., Wilson, J. and P. Dick. 2001. Efficacy of narasin in the prevention of necrotic enteritis in broiler chickens. *Avian Dis.* 45: 210-214.

Callender, M.E. and T.K. Jeffers. 1980. Anticoccidial combinations comprising nicarbazin and the polyether antibiotics. U.S. Patent Number 4,218,438.

Callender, M.E., Bentley, E.J. and R.F. Shumard. 1987a. Floor pen trials with the anticoccidial combination of narasin and nicarbazin: Dose titration trials in Europe and the U.S. *Poult. Sci.* 66: (Suppl.) 1: p. 74.

Callender, M.E., Donovan, D.J., Tonkinson, L.V. and R.F. Shumard. 1987b. Dose titration of the anticoccidial combination of narasin and nicarbazin. *Poult. Sci.* 66: (Suppl.) 1: p. 74.

Chapman, H.D. 1976. *Eimeria tenella* in chickens: studies on resistance to the anticoccidial drugs monensin and lasalocid. *Vet. Parasitol.* 2: 187-196.

Chapman, H.D. 1978. Drug resistance in coccidia. In: *Avian Coccidiosis*, Long, P.L., Boorman, K.N. and B.M. Freeman (eds.) p. 387. British Poultry Science, Ltd., Edinburgh.

Chapman, H.D. 1982. Anticoccidial drug resistance. In: *The Biology of the Coccidia*, P.L. Long (ed.). p. 429, University Park Press, Baltimore.

Chapman, H.D. 2003. Personal communication.

Dykstra, D. and Reid, W. Monensin, *Eimeria tenella* infection, and effects on the bacterial population of gnotobiotic chickens. *Poultry Sci.* 57, 1978.

Hembolt, C.F. and Bryant, E.S. 1971. The pathology of necrotic enteritis in domestic fowl. *Avian Dis.* 15: 775-780.

Jeffers, T.K. 1974a. *Eimeria tenella*: Incidence, distribution and anticoccidial drug resistance of isolants in major broiler producing areas. *Avian Dis.* 18: 74-84.

Jeffers, T.K. 1974b. *Eimeria acervulina* and *Eimeria maxima*: Incidence and anticoccidial drug resistance of isolants in major broiler producing areas. *Avian Dis.* 18: 331-342.

Jeffers, T.K. 1978. Genetics of coccidia and the host response. In: *Avian Coccidiosis*, Long, P.L., Boorman, K.N. and B.M. Freeman (eds.) p. 51. British Poultry Science, Ltd., Edinburgh.

Jeffers, T.K. 1981. Resistance and cross-resistance studies with narasin, a new polyether antibiotic anticoccidial. *Avian Dis.* 25: 395-403.

Jeffers, T.K. 1989. Anticoccidial drug resistance: a review with emphasis on the polyether ionophores. In: Coccidia and intestinal coccidiomorphs. *Proc. 5th Int. Coccidiosis Conf.* P. Yvore (ed.) INRA Publ. Pp. 295-308.

Jeffers, T.K. and M.W. Shirley. 1982. Genetics, specific and intraspecific variation. In: *The Biology of the Coccidia*, P.L. Long (ed.) p. 63. University Park Press, Baltimore.

McDougald, L.R. 1982. Chemotherapy of coccidiosis. In: *The Biology of Coccidia*. P.L. Long (ed.) Univ. Park Press. Baltimore. p. 373-427.

McDougald, L.R. 2003. Personal communication.

McDougald, L.R., Fuller, A. L. and R. Mattiello. 1997. A survey of coccidia on 43 poultry farms in Argentina. *Avian Dis.* 41: 923-929.

McDougald, L.R., Fuller, A.L. and J. Solis. 1986. Drug sensitivity of 99 isolates of coccidia from broiler farms. *Avian Dis.* 30: 690-694.

McDougald, L.R., Da Silva, J. M. L., Solis, J. and M. Braga. 1987. A survey of sensitivity to anticoccidial drugs in 60 isolates of coccidia from broiler chickens in Brazil and Argentina. *Avian Dis.* 31: 287-292.

McLoughlin, D.K. and M.B. Chute. 1974. The efficacy of monensin against one sensitive and thirteen drug resistant strains of Eimeria tenella. *Poult. Sci.* 53: 770-772.

Mitrovic, M. and E.G. Schildknecht. 1975. Lasalocid: resistance and cross-resistance studies in *Eimeria tenella* infected chicks. *Poult. Sci.* 54: 750-756.

Radostits, D.M. and Stockdale, P.H. 1980. A brief review of bovine coccidiosis in Western Canada. *Can. Vet. J.* 21:227.

Ryley, J.F. 1980. Drug resistance in coccidia. *Adv. Vet. Sci. Comp. Med.* 24: 99-120.

Ryley, J.F. and M.J. Betts. 1973. Chemotherapy of chicken coccidiosis. *Adv. Pharmacol. Chemotherapy* 11: 221-293.

Shumard, R.F. and M. E. Callender. 1969. Effectiveness of monensin against experimentally induced coccidiosis in battery raised chickens. *Poult. Sci.* 48: 1870-1871.

Smith, C.K. and R.B. Galloway. 1983. Influence of monensin on cation influx and glycolysis of *Eimeria tenella* sporozoites in vitro. *Journ. Parasitol.* 69: 666-670.

Smith, C.K., Galloway, R.B. and S. L. White. 1981. Effect of ionophores on survival, penetration and development of *Eimeria tenella* sporozoites in vitro. *Journ. Parasitol.* 67: 511-516.

Smith, C.K. and R.B. Strout. 1979. *Eimeria tenella*: accumulation and retention of anticoccidial ionophores by extracellular sporozoites. *Exp. Parasitol.* 48: 325-330.

Tonkinson, L.V., Jeffers, T.K. and M. E. Callender. 1987. Anticoccidial efficacy of various ratios of narasin and nicarbazin. *Poult. Sci.* 66: (Suppl.) 1: p. 87.

Watkins, K.L., Shryock, T.R., Dearth, R.N. and Y.M. Saif. 1997. In vitro antimicrobial susceptibility of Clostridium perfringens from commercial turkey and broiler chicken origin. *Vet. Microbiol.* 54: 195-200.

Weppleman, R.M., Battaglia, J.A. and C.C. Wang. 1977. Eimeria tenella: The selection and frequency of drug resistant mutants. *Exp. Parasitol.* 42: 5666.

Elanco Animal Health

2500 Innovation Way
Greenfield, IN 46140

USPBUMXN00031

FULL VALUE POULTRY™

Elanco™

1-800-428-4441
www.elanco.com

NOTES

NOTES

NOTES