

## Anticoccidial Drugs Used in the Poultry: An Overview

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### ABSTRACT

Coccidiosis is severe disease and important from an economic point of view in poultry industry. So, proper control measures should be followed for its prevention of occurrence. Control measures include good husbandry, as a prime requirement and the use of anticoccidial drugs for both prophylaxis and treatment. For the drug to be effective anticoccidial, it should be used prophylactically instead of therapeutically. Most of the anticoccidials show their greatest efficacy against the 1st and 2nd asexual cycle, some inhibits sexual stages of the life cycle. Selection of an anticoccidial is based on the ability of the drug to improve weight and feed conversion and to suppress the development of lesions. The emergence of drug resistant strains of coccidia presents a major problem. So, to avoid the development of drug resistance a method is used which include switching around different classes of drugs and the 'shuttle programme'. In present overview, we are discussing about some anticoccidials used for the prevention and control of coccidial infection by affecting different stages of life cycle of coccidia. The common anticoccidials/class of anticoccidials are ionophores, amprolium, sulphonamides, ethopabate, clopidol and quinolones.

**Key words:** Coccidiosis, anticoccidial drugs, economic, resistant strain, shuttle programme

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### INTRODUCTION

Gastrointestinal parasitism is one of the most important constraints for the growth and developments of poultry industry in world including India. These parasites cause heavy economic losses to farmers by affecting growth, production and high mortality and mortality amongst young animals. In gastrointestinal parasitism coccidian infection plays an important role, various species reported from the chicken are *Eimeria acervulina*, *E. brunette*, *E. necatrix*, *E. tenella*, *E. maxima*, *E. mitis*, *E. mivati* and *E. hagani* etc. These species have predilection site in the different part of gastrointestinal tract. *E. acervulina* occurs in the epithelial cells of the anterior portion of the small intestine mainly in duodenum. *E. brunette* occurs in the mucosa of the lower

portion of the small intestine, caecum, rectum and cloaca. *E. tenella* is present in caecum. *E. necatrix* occurs in the jejunum, mid gut, caecum and other parts of the large intestine. They produce severe damage to the site of their predilection in various mammals including human being. In general, there are three types of coccidiosis occur depending on the site of predilection of causative agents:

- Intestinal coccidiosis due to *E. necatrix*, *E. maxima*, *E. mivati*, *E. acervulina*
- Caecal coccidiosis primarily due to *E. tenella* and to some extent *E. necatrix*
- Rectal coccidiosis due to *E. brunetti*. *E. tenella* is most pathogenic coccidia and causes severe disease of poultry rated next to that caused by *Salmonella pullorum*

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Life cycle of avian coccidian consist of 2 asexual cycles which collectively require one or more days. The life cycle consist of various stages which involve oocyst-sporozites-trophozoites-schizonts (completion of 1st asexual cycle)-merozoites-trophozoites-schizonts (completion of 2nd asexual cycle)-merozoites-formation of male and female gametes (sexual cycle)-sporulating oocyst (outside the host). Whole life cycle requires 7 days for completion. Short life cycle and large number of sporulating oocyst of parasites helps in increasing the chance of contamination to a large population. Coccidiosis is important from an economic point of view, where the birds are raised under intensive conditions. The severity of the disease which occurs depends both on the infecting species and the density of parasite burden. As prevention is greater than treatment, so proper control measures should be followed. Control measures include good husbandry, as a prime requirement and the use of anticoccidial drugs for both prophylaxis and treatment.

**Anticoccidial drugs:** The agents used for the prevention and control of coccidia infections are termed as anticoccidial drugs. The agents who destroy the coccidial population are termed as coccidiocidal and agents who prevent the replication and growth of coccidial population are known as coccidiostatic. To make the anticoccidials effective, it should be used prophylactically instead of therapeutically. Some anticoccidials show strong activity during the sexual cycle i.e., day 5 and 6 and during these days signs of anorexia and hemorrhage appear so initiating anticoccidials treatments during these days will provide more benefit. Anticoccidials are used usually in starter rations for meat type birds raised under floor-pen management.

Most of the anticoccidials show their greatest efficacy against the 1st and 2nd asexual cycle, some inhibits sexual stages of the life cycle. Only few anticoccidials disturb the chemical metabolic pathway by which the drug block the specific stage of the parasite<sup>1</sup>. Selection of an anticoccidial is based on the ability of the drug to improve weight and feed conversion and to suppress the development of lesions<sup>2</sup>. Presence of drug residues in eggs and milk is also a point of concern associated with the anticoccidials, so there is need for specified withdrawal periods before slaughter. The emergence of drug resistant strains of coccidia presents a major problem. To avoid the development of drug resistance there is method used which include switching around different classes of drugs and the 'shuttle programme'. Many therapeutic regimens are to maximize the efficiency of treatment and to minimize the possibility of resistance e.g. anticoccidial drugs given in sub therapeutic doses to encourage the development of

immunity and the use of compound anticoccidial preparations are common. The speed of emergence of resistant strains of coccidia in the field is given by Reid (1975) as follows: (1) Glycomide-very rapid, (2) Quinolones-rapid, (3) Clopidol-less rapid, (4) Sulphonamides, nitrofurons, robenidine-moderate, (5) Amprolium-slow, (6) Nicarbazine-very slow and (7) Monensin-absent or very slow. Resistance is more likely to develop in birds reared under intensive conditions than in farm animals<sup>3</sup>. Present overview discuss briefly about various anticoccidials used for the prevention and control of coccidial infection by affecting different stages of life cycle of coccidia.

**Ionophores:** Ionophores are the fermentation products of *Streptomyces* and other fungi species, extensively used as anticoccidials. Monensin, Lasalocid and Salinomycin are the Ionophores which are used commercially and monensin is choice of product for broiler chickens mainly because of its broad spectrum activity against majority of pathogenic species of coccidian and lack of development of drug resistance.

**Mechanism of action:** Ionophores facilitate transport of  $\text{Na}^+$  ion in cells and elevates the intracellular concentration of  $\text{Na}^+$  ion. This increased concentration of  $\text{Na}^+$  ion inhibits the certain mitochondrial functions such as substrate oxidation and ATP hydrolysis. Intracellular  $\text{Na}^+$  ion exchanges for extracellular  $\text{Ca}^{++}$  and increases intracellular concentration of calcium ions lead to cytotoxicity. In addition some drugs directly facilitates  $\text{Ca}^{++}$  transport in cells and increased intracellular concentration of  $\text{Ca}^{++}$  in cardiac and skeletal muscle cells are responsible for its toxic effects in cells.

**Monensin:** It is a fermentation product of *Streptomyces cinnamomensis* and the 1st antibiotic used as an anticoccidials. Due to its broad spectrum activity, it acts on trophozoites and 1st generation schizonts. Its activity is generally within 1st 2 days of life cycle of coccidian. It gives protection against all species at 0.01-0.121% concentration in the feed. It also increases the weight gain and feed conversion and in some cases causes suppression of necrotic enteritis<sup>2</sup>. It is superior over amprolium, clopidol and zoalene in control of coccidiosis. In the USA, there is a three day premarketing withdrawal requirement for this compound. This drug has ability to form complexes with sodium and potassium ions in the host and developing parasite. This monensin-cation complex renders membrane permeability to sodium and potassium ions.

**Lasalocid:** It is another fermentation product and has a high degree of anticoccidials activity. It is effective at 0.005-0.0075% concentration. It also increases weight

gain, feed conversion and reduces the lesion in severe coccidiosis<sup>2</sup>. It has different ionic affinities and accepts divalent cations as well as monovalent ions.

**Salinomycin:** It was isolated from a culture of *Streptomyces albus*. It is more closely related to monensin than lasalocid. It has anticoccidial activity at 0.01% in the feed and it was as effective as 0.0121% monensin in controlling coccidiosis<sup>4</sup>. The ionic affinity is similar to that of monensin i.e. sodium and potassium ions.

**Maduramicin:** It is most potent among the polyether Ionophores. It is given at 5-6 ppm in feed and activity is similar to that of other Ionophores<sup>5</sup>. Problem of these Ionophores is that they may cause severe cardiovascular defects in animal cells.

**Amprolium:** [1-(4-amino-2-n-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride]: it is quaternized derivative of pyrimidine which is a thiamine antagonist. It is most active against *E. tenella*, *E. necatrix* and *E. acervulina* and to lesser extent *E. maxima*. Combination of amprolium with ethopabate, sulphaquinoxaline or even pyrimethamine extended and strengthened the spectrum of activity. It could be fed at several times the recommended dose with no ill effects and probably, one of the safest antimicrobial drugs to be used extensively. It is effective against 1st generation of trophozoites and schizonts and shows peak activity early in day 3 of cycle. It also suppresses the sexual stages, gametogony and sporulation of oocyst. Continuous use of Amprolium is resulting into the development of drug resistance which is a major problem and limiting its use. It is rarely used alone because *E. maxima* and other species are resistant and therefore given in combination with other drugs. Amprolium is available as a premix and is given prophylactically to birds in a final concentration of 0.0125 percent. In combination with 2 other drugs, it is given at a level of 0.006% of each in the food with better effectiveness<sup>6</sup>. A combination of amprolium and sulphaquinoxaline at levels of 0.006% of each in the food is more effective against poultry coccidiosis than either of the two drugs used alone<sup>7</sup>. There is no premarketing withdrawal requirement for this compound. Amprolium is compatible with vitamins, antibiotics, minerals and other ingredients commonly used in poultry ration but it should not be mixed in concentrates containing high levels of choline because of tendency for it to break down into picric acid.

**Mechanism of action:** It is thiamine antagonist and due to its close structural similarity it blocks the thiamine receptors. This blockage of receptors prevents coccidia from utilizing thiamine and as a result thiamine is

unavailable to coccidia. This vitamin (thiamine pyrophosphate) is a cofactor of several decarboxylase enzymes which play role in cofactor synthesis. It is only agent which can be used in laying birds both for prevention and treatment of outbreaks. At higher doses, thiamine deficiency can occur in host but it can be prevented by addition of thiamine.

**Nicarbazine:** This drug is an equimolecular complex of p, p'-dinitrocarbanilide (DNC) and 2-hydroxy-4, 6-dimethylpyrimidine (HDP). DNC is absorbed more rapidly from the chicken digestive tract but disappears more slowly from the tissues than HDP. Both are necessary for anticoccidial activity. This compound is used principally as a prophylactic and therapeutic dose lies near the toxic dose. Nicarbazine is having broad spectrum activity and effective against all *Eimeria* spp. This compound has coccidiocidal activity, mainly against the schizonts which appear after the 1st generation. Marked inhibitory effect on the second generation schizonts and moderate action on the sexual stages have been reported by McLoughlin and Wehr<sup>8</sup>. It is available as a 22.5% premix and it is incorporated into feed to bring a final concentration of 0.0125%. It is coccidiocidal principally because its molecules can enter the cells of the coccidia and paralyze the intracellular energy-supplying ATP which leads to the interruption of cellular energy supply and the cease of function of sodium-potassium ion pump which results in the abundant influx of sodium ions and with them the influx of abundant water which causes the intracellular imbalance of ions in the cells of the coccidia or the rupture of the cells and the death of coccidia occurs. Some strains of coccidia which have become resistant to other drugs remain sensitive to nicarbazin. The drug is suitable for administration to broiler flocks and it is usually given for the first 12 weeks of the chicken's life. It reduces both egg production and the proportion of fertile eggs that hatch. It also causes depigmentation of eggs, mottled egg yolk and poor hatchability, so it should not be used for laying hens. In broilers, a 4 day withdrawal of nicarbazin is required before marketing. Losses from heat stress may occur in broilers if they are medicated with nicarbazin.

**Sulphonamides:** They have longest history of use as anticoccidial drugs. The common drugs of this group which are used as anticoccidials are sulphadimidine, sulphaquinoxaline, sulphadimethoxine, sulphamethoxazole and sulphaguanidine. Sulphonamides have broad spectrum of activity against eimerian species and have coccidiostatic action. They are used for prevention and treatment of coccidia and in outbreaks. They are more effective against intestinal than caecal forms of coccidia. They stop the

onset of the disease by acting against the second generation schizonts of *E. tenella* and *E. necatrix*. They can act upon first generation schizonts and possibly against sexual stages but much higher doses are required. Use of these drugs does not impair immunity development.

**Mechanism of action:** Wood and Fildes proposed mechanism of action of sulphonamides, coccidian is synthesizing their own folic acid utilizing PABA (p-amino-benzoic acid) from growing medium because folic acid is required for growth/replication of DNA<sup>9</sup>. Sulfonamides are structural analogues (PABA and Sulfonamide is similar in nature) of PABA inhibit bacterial folate synthetase resulting into folic acid is not formed and a number of essential metabolic reactions suffer. Animal cells also require folic acid but they utilize performed folic acid supplied in diet and are unaffected by sulfonamides. Therefore they prevent proper development of schizonts. Diaminopyrimidines inhibits the conversion of folic acid to tetrahydrofolic acid and are used in combination with Sulphonamides to potentiate their anticoccidial action.

**Sulphadimidine:** This compound is still used as a curative drug in certain parts of the world, but its use has largely been discontinued in Western Europe and North America where it has been replaced by other compounds<sup>10</sup>. It is given @ 0.4% in feed or in drinking water as 0.2% solution of the sodium salt. It is active against *E. tenella*, *E. necatrix* and other species of coccidia. It has been used in the control of clinical outbreaks of coccidiosis. The problem of this drug is that it interferes with vitamin K synthesis in the intestine and resulting into prolongation of blood coagulation time. At higher doses it causes loss of egg production in laying hens and hyperplasia of the somniferous tubules of testicles of male birds.

**Sulphaquinoxaline:** It is an important, effective and commonly used coccidiostat throughout the world. For therapeutic purposes a dose of 0.5% in the feed is given. In drinking water, a dose of 0.043% is given for two durations each for 2 days with 3-5 days intervals, is satisfactory. Doses ranging from 0.025 to 0.033% over fairly long periods may be used as preventive medication. It is also active against *E. acervulina* in addition to *E. necatrix* and *E. tenella*. It exerts marked inhibitory effects on schizogony. Drug at a level of 0.1% in the ration inhibited invasion by the sporozoites<sup>11</sup>. When used at higher dose for long duration it produces toxic effects which include multiple hemorrhages in many organs accompanied by necrotic lesions in the spleen, hypoplasia of bone marrow and agranulocytosis<sup>12</sup>. This toxicity is associated

with an interference with vitamin K metabolism. This compound has 6 days withdrawal premarketing requirement and eggs from treated birds should not be used for human consumption.

**Ethopabate:** It is an arylamide containing one phenyl ring, belonging to monocyclic aromatics, is a very safe drug. It has anticoccidial activity especially against intestinal forms and lacks activity against *E. tenella* of caecal worms. This drug is a competitor of PABA for absorption by the parasite and interferes with folate synthesis. It has good activity against *E. acervulina* and some strains of *E. maxima* and *E. brunette*. It has been used only in combination with Amprolium first at 4 ppm and later at 40 ppm. This drug has peak activity on 4<sup>th</sup> day of cycle.

**Clopidol:** It is the only member of its class i.e. pyridinols having useful anticoccidial properties. It is also called metichlorpindol or clopidol. It has broad spectrum activity. It is almost completely coccidiostatic in action and effects the sporozoites or trophozoites. It is most active against the sporozoite stage of *Eimeria*. Thus to produce full anticoccidial potential, it should be in the feed of chickens on the day of exposure to coccidial oocyst. Day one of the coccidia cycle is designated as day of peak activity for clopidol. Drug is not active if given after day of exposure, so should be given on day first. Its coccidiostatic activity holds the sporozoites undeveloped in an epithelial or host macrophages cells for as long as 60 days. Latent coccidiosis may appear if drug is withdrawn during the static state, as the parasites resume development. This drug is generally administered at 125 ppm in the feed. It may be used in last 1-3 weeks of the broiler grow out. There is no premarketing withdrawal requirement.

**Quinolones:** There are hundreds of Quinolones which have been synthesized and a number of them have showed activity against various groups of parasites. Buquinolate, decoquinolate and nequinolate are the examples of Quinolones which have shown great efficacy against all species of poultry coccidia. Quinolones have limited absorption because they are virtually insoluble in water. Tissue residues of Quinolones are very low and the liver is the main organ which has greatest concentration. They act on the sporozoite stage of the life cycle of coccidian. The sporozoite is evidently able to penetrate the host intestinal cell but its further development is prevented. Thus on day 1st of life cycle, these compounds show maximum activity. So, these drugs must be in feed on day one of exposure to coccidia to give maximum advantages.

**Mechanism of action:** Anticoccidial activity of these compounds depends on disruption of electron transport in cytochrome system of mitochondria in coccidia while decoquinone inhibits DNA synthesis by inhibiting DNA gyrase and not effective in treatment of clinical coccidiosis. Quinolones is a class of anticoccidials which is not able to give complete control of oocyst production. The compounds of this class are not able to completely eliminate the oocyst which enhances the potential for the development of drug resistant strains of coccidia. Thus their use in chicken as anticoccidials is now limited.

**Buquinolate:** It has broad spectrum of activity against all chicken coccidia. It arrests sporozoite development but does not kill these forms. The inhibited stages may recommence development if it is withdrawn too early. It is given at the level of 0.00825% in the feed. It favourably increases the feed conversion rates. This drug has low toxicity and elimination rate is fast from the tissues following withdrawal of medicated feed<sup>13</sup>.

**Decoquinone:** It also has broad spectrum coccidiostat activity and inhibits sporozoite development. It is used at a concentration of 0.003% in the feed. This compound has no premarketing withdrawal requirements.

**Robenidine:** It is a guanidine derivative and not available in the USA but is used to some extent in Europe and South America. It is a broad spectrum coccidiostatic and coccidiocidal drug, used for the prophylaxis of coccidiosis. It inhibits oxidative phosphorylation in late first generation and second stage schizonts. It may also have an effect on the gametocytes. It is most effective against the maturing first generation schizonts. It is effective as 0.0066% mixture in the feed. It is not used in laying hens and has 5 day withdrawal period for the slaughter of poultry. It imparts unpleasant taste to the flesh of broiler birds if not withdrawn for 5 days before slaughter.

**Halofuginone:** Halofuginone is a quinazolinone derivative. It is an alkaloid originally isolated from the plant *Dichroa febrifuga* and tested for antimalarial activity in China many years ago. This drug has potent broad spectrum coccidiocidal and coccidiostatic activity against 1st and 2nd generation schizonts. The mechanism of action against *Eimeria* spp. is unknown at present. It is used for the prevention of coccidiosis and should only be given to young birds (up to 12 weeks of age for poultry). The drug is effective against pathogenic eimerian species in chicken at a feed concentration of 3 ppm. The drug is not given to the egg laying birds and has 5 days withdrawal period for the slaughter.

## CONCLUSION

It would not have been feasible to develop the modern chicken and turkey industries without the discovery and use of anticoccidials. These anticoccidials are extremely effective and enable the animal to achieve optimum performance by remaining free of the debilitating coccidiosis disease, when used in a structured and monitored programme.

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