International Journal of Pharmaceutical Chemistry and Analysis 2021;8(4):159–166

Content available at: https://www.ipinnovative.com/open-access-journals

International Journal of Pharmaceutical Chemistry and Analysis

Journal homepage: https://www.ijpca.org/

Review Article

Pharmacotherapy of gastrointestinal strongylosis of small ruminants: An update

Deto UJ-P N'guessan[1], Songuigama Coulibaly[1], Mahama Ouattara[1,*]

[1] *Dept. of Therapeutic and Organic Chemistry, UFR Pharmaceutical and Biological Sciences, Félix Houphouët-Boigny University, Abidjan, Côte d'Ivoire*

ARTICLE INFO

Article history:
Received 26-10-2021
Accepted 18-11-2021
Available online 25-01-2022

Keywords:
Anthelmintics
Chemoresistant
Gastrointestinal
Strongylosis

ABSTRACT

Gastrointestinal strongylosis, which causes deadly seasonal diarrhea in small ruminants, is a major threat to the livestock population in sub-Saharan Africa. Moreover, livestock is a central component of food security. In addition to this threat, there is a poor veterinary coverage due to the increasing lack of effective anthelmintic drugs against strongyles because of the emergence and proliferation of chemo resistant strains. In this context, and given that the use of a vaccine is not widespread, the establishment of the therapeutic arsenal available to veterinarians to control strongyles will contribute to the food and economic security of rural populations. This review outlines the main pharmacochemical classes of anthelmintics used in the management of strongylosis of small ruminants.

1. Introduction

The gastrointestinal strongylosis of small ruminants or digestive strongylosis are parasitic diseases caused by nematodes within the herd, especially in sheep and goats.[1] These digestive helminthoses usually evolve during the grazing period and mainly result in gastroenteritis with rebellious diarrhea or the evolution of anemic syndrome.[2] In fact, their wide geographical distribution and their pathogenic nature lead to significant economic losses in flocks.[3] The threat of gastrointestinal parasitosis in small ruminants is all the more alarming as livestock production contributes to 8 to 15% of the Gross Domestic Product (GDP) in West Africa. Moreover, grazing ruminants production accounts for 34% of the cash income of rural households.[4] The objective of most animal parasite control strategies is not to eliminate the offending pests altogether, but to keep the infesting population below a threshold above which it would inflict harmful effects on the host population.[5] Anthelmintic drugs are commonly used for either prophylactic purposes, in which timing of treatment is based on knowledge of epidemiology, or for therapeutic purposes to treat existing infections or clinical epidemics. Since the advent of anthelmintics, considerable progress has been made in the use of various animal pest medications.[6–8] The aim of this review is to present the pharmacochemical aspects of anthelmintics currently used for the management of strongylosis in small ruminants and the perspectives of drug research for this parasitosis.

1.1. History and classification

Many chemical compounds and plant metabolites have toxic effects on parasitic nematodes. Although most, including drugs such as sodium arsenite, tetrachlorethylene, carbon tetrachloride, carbon disulfide, copper sulphate and nicotine sulphate, were used earlier, these deworming drugs are potentially as toxic to parasites as to their hosts. The economic importance of breeding led to the development in 1939 of the first synthetic anthelmintic,

* *Corresponding author.*
E-mail address: mahama.ouattara@univ-fhb.edu.ci (M. Ouattara).

https://doi.org/10.18231/j.ijpca.2021.031

Phenothiazine or Thiodiphenylamine (Figure 1).[9] The introduction of phenothiazine into therapeutics, followed in the early 1960s, by the discovery and development of the first benzimidazole drug with a broader spectrum of action on gastrointestinal nematodes. Thiabendazole has helped to make sheep production profitable in some parts of the world.[10]

In addition to benzimidazoles, several other anthelmintics have been discovered and placed on the market, including imidazothiazoles. The first drug in this class of nicotinic receptor agonist, levamisole, was introduced in the early 1970s.[11] In 1977, a new anthelmintic of the salicylanilide class was discovered: Closantel.[12] Therefore, Closantel and Nitroxinil from the nitrophenol group (discovered in 1966) are available and have a narrow spectrum of activity against H. contortus.[13]

From 1975, research on antiparasitics was directed to substances of natural origin, radically different from those used in veterinary therapy. This led to the discovery of the chemical class of macrocyclic lactones which are polyvalent antiparasitic active both in human medicine, especially in filariasis and veterinary medicine against gastrointestinal and respiratory nematodes in ruminants, equines, swine and the domestic animals. The first macrocyclic lactone drug, ivermectin, was discovered by Satoshi Omura and William Campbell and introduced therapeutically in the early 1980s.[14] In 2015, these researchers received the Nobel Prize for Medicine for this groundbreaking discovery.[15]

One of the last anthelmintic molecules that was developed in 2008 is Monepantel. This represents the precursor of a fifth family introduced on the market, that of the amino-acetonitrile derivatives and was presented as a solution in case of multiple resistance to anthelmintics.[16] Other drugs such as Derquantel (spiroindole), in combination with abamectin are also used. In total, according to their mode of action, the chimioth ed therapy of strongylosis ruminants traditionally based on four main pharmacological classes of broad-spectrum anthelmintics that are:

1. The benzimidazoles inhibiting the polymerization of β-tubulins,
2. Cholinomimetic imidazothiazoles and tetrahydropyrimidines,
3. The macrocyclic lactones activating the glutamate-dependent chloride channels,
4. Salicylanilides and nitrophenols as inhibitors of oxidative phosphorylation

To those, we should add the chemical classes of amino acetonitriles, the spiroindoles and cyclooctadepsipeptides that contain molecules used in combination with other pesticides.

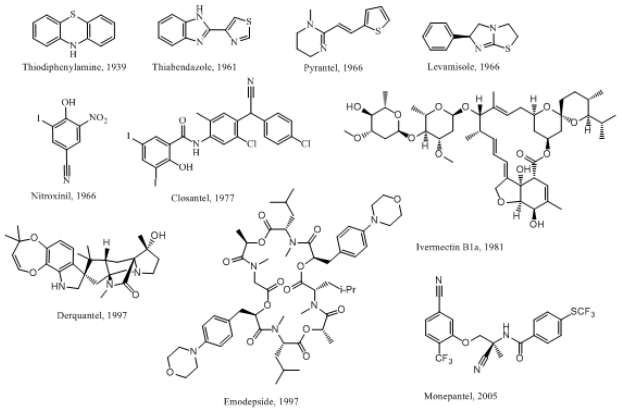

Fig. 1: Main anthelmintics

2. Classical Anthelmintics

2.1. Benzimidazoles and probenzimidazoles

2.1.1. Definition-Structure

Benzimidazoles and anthelmintic probenzimidazoles have the distinction of being used in both human medicine and veterinary medicine. This chemical series is characterized by the presence of the benzimidazole ring used as a heterocyclic support.[17] It includes four subgroups, however benzimidazoles available in small ruminants belong to the first two categories of compounds[18] (Figure 2) **:**

1. Probenzimidazoles which have the ability to release the corresponding benzimidazoles as active metabolites in a biological medium. Developed to improve the solubility of benzimidazoles in water and their absorption, they have 2 representatives in veterinary medicine : Febantel and Nétobimin.
2. The 2-carbamoyl-benzimidazoles derivatives, substituted in position 2 by a carbamate and in position 5 by various modulators. They are the most numerous and the most important. Those used in veterinary medicine are: Albendazole, Oxfendazole, Fenbendazole, Oxibendazole, Flubendazole and Mebendazole (in combination).
3. A derivative substituted in position 2 by a thioether function, in position 5 by a halogen and in position 6 by a phenoxyl group: Triclabendazole
4. A Derivative substituted in position 2 by a thiazole-type heterocycle: Thiabendazole

They are marketed in the form of oral powder, oral and injectable solutions or suspensions, intraruminal boluses or medicated premixes.[18]

2.1.2. Mechanism of action

Benzimidazoles act directly on the worms while probenzimidazoles are administered to the animal in the form of prodrugs converted into active molecules by

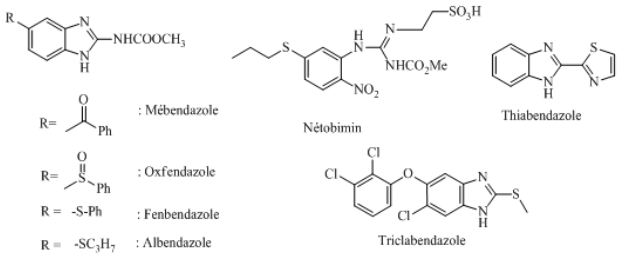

Fig. 2: Structures of some benzimidazole and probenzimidazole anthelmintics

enzymatic reactions, which generally take place in the liver.[6]

These drugs would bind to β-tubulin proteins in the cytoplasm of intestinal nematode cells, thereby inhibiting dimerization with α-tubulin during microtubule formation without altering those of host.[19] Since microtubules are the structural base of the cytoskeleton, these molecules induce lesions of the intestinal cells in the worm and thus stop the worms' feeding. The nematodes thus susceptible die of hunger.[20] In addition, these drugs are ovicidal, by inhibiting the hatching of nematode eggs by a destructive antimitotic effect of the microtubule network of the parasite without altering that of the host.[6]

2.1.3. Spectrum of action and indications

In veterinary medicine, benzimidazole derivatives are used in the treatment of respiratory nematode infections (especially against worm bronchitis due to strongyles), ascariasis, strongylosis of the small intestine and the large intestine. For digestive strongyloses, benzimidazole derivatives are not only active on adult forms, but also on immature forms. The most sensitive genera are Haemonchus, Ostertagia, Trichostrongylus, Cooperia, Nematodirus , Chabertia and Oesophagostomum.[21]

Table 1 Summarizes the action spectra of all active anthelmintic molecules in gastrointestinal strongyles.

2.2. Macrocyclic lactones

2.2.1. Definition — structure

Macrocyclic lactones represent a homogeneous family of anthelmintics of natural origin. They are endectocides derived from actinomycete fermentation of the genus Streptomyces. The species Streptomyces avermitilis, Streptomyces hygroscopicus and Streptomyces cyaneogriseus generate during their growth many compounds that fall into two sub-families: avermectins (eg Ivermectin (Figure 3), Doramectin, Abamectin etc.) and milbemycins (eg Moxidectin).[21] The name avermectin derives from its properties acaricide, insecticide and nematocide: a for anti, verm for worm and ect for ectoparasite.[22] Abamectin (avermectin B1) is more active on nematodes than Ivermectin but less effective on arthropods.

From the point of view of their chemical constitution, they are 16-membered macrolides which all have a complex structure comprising a lactone heterocycle. The major structural difference between the two groups is the presence of the disaccharide moiety (bisoleandrosyloxy substituent) on carbon number 13 (C^{13}) avermectins. Milbemycins are deprived of it; they are therefore deglycosylated avermectins (aglycones of avermectins) (Figure 3).[23] α-milbemycins retain the furan ring while for β, the C^6-O bond no longer exists.

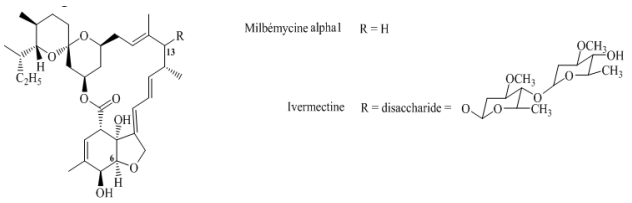

Fig. 3: Structure of Milbemycin α-1 and Ivermectin

2.2.2. Mechanism of action

Despite the structural differences between avermectins and milbemycins, the main mechanism of action is similar and involves activation of the glutamate-dependent chloride (GluCl) channels of the neuromuscular cell membrane of nematode (absent in mammals).[6] Incidentally, they have effects on gamma-aminobutyric acid (GABACl) receptors. This allosteric binding to the subunits of the GluCl and GABACl channels would cause their opening and an increase in membrane permeability to chloride ions, which is time-dependent.[20] Then occur paralysis pharynx and somatic muscle and death of nematodes.[23] In addition, a study of Caenorhabditis elegans revealed that the levamisole-sensitive receptor (L-AChR), one of the major excitatory receptors involved in parasitic locomotion, is profoundly inhibited by ivermectin.[20] This would lead to a hyperpolarization of nerve and muscle cells causing reduction of pharyngeal pumping, flaccid paralysis of muscles and effects on the body of the uterus. These effects result in an inability to feed, move or lay eggs, respectively.[24,25]

It has been proven that apart from this classical mechanism of action, Ivermectin and Moxidectin have an action mediated in part by PGP transport proteins.[26]

2.2.3. Spectrum of action and indications

Macrocyclic lactones are indicated for the treatment of gastrointestinal, respiratory and renal nematodoses in ruminants. The most sensitive parasites are strongyles (*Bunostomum, Charbertia, Haemonchus, Oesophagostomum, Ostertagia ostertagi, Trichostrongylus* adult

Table 1: Main families, anthelmintic molecules and their spectrum of action against the main gastrointestinal nematodes of small ruminants

Families	Anthelmintics	Action spectrum
Benzimidazole	All	Ad, L4 and hypobiosis of Hc and Tc
Imidazothiazoles	Levamisole	Ad and L4 of Hc and Tc
Tetrahydropyrimidine	Pyrantel	Ad
Salicylanides	All	Ad, L4 and hypobiosis of Hc
Nitrophenols	Nitroxinil	Ad, L4 and hypobiosis of Hc
Lactones macrocyclic	Ivermectin doramectin moxidectin	Ad and L4 of Hc, Tc and Ta Ad, L4 and hypobiosis of Hc and Tc Ad, L4 and hypobiosis of Hc, Tc and Ta
Cyclooctadepsipeptides	Emodepside	Ad and L4 of Hc
Spiroindoles	Derquantel (+ Abamectine)	Ad, L4 and hypobiosis of Hc, Tc and Ta + Resistant and multiresistant Nematodes
Aminoacetonitrile derivatives	Monepantel	Ad, L4 and hypobiosis of Hc, Tc, Ta,

Ad: adult; L4: 4eme stade larvaire, Hc: Haemonchus contortus ; Tc: Teladorsagia circumcincta ; Ta: Trichostrongylus axi

and immature).[22] Moxidectin has the distinction of being effective and protecting against reinfestations by abomasum parasites for at least 5 weeks[23] (Table 1).

2.3. Salicylanides

2.3.1. Definition- structure

Salicy lanilides represent a homogenous class of anthelmintics, characterized by an amide function resulting from condensation between salicylic acid derivatives and aniline. The substituents of the phenyl groups are most often groups recognized as contributing to antiseptic or antiparasitic activities. : halo (Cl, Br, I), nitro, p-chlorophenoxyl.[17] This family includes four molecules but only one is currently used in the treatment of strongyles in ruminants (Figure 1).[18]

2.3.2. Mechanism of action

At therapeutic doses, they are proton ionophores, specifically decoupling the mitochondrial oxidative phosphorylation of Adenosine Diphosphate (ADP), thus decreasing the synthesis of adenosine triphosphate[19,21] (ATP). Enzymatic systems are then disturbed, resulting in energy depletion. In addition, the resulting blockage of the Krebs cycle results in the accumulation of lactic acid. This accumulation severely increases the disturbances of parasite metabolism which becomes sensitive to the proteolytic enzymes of the host.[17] The action is immediate and prolonged (up to 35 days against *H. contortus*), because these molecules are highly related (> 99%) to plasma proteins.[19]

2.3.3. Spectrum of action and indications

These compounds are mainly used as douvicides but some of them are nematocides. They are active against *H. contortus*. Closantel is also very effective against adult-onset haematophagous strongles such as *Haemonchus* and *Bunostomum* in sheep. It is used as a substitute drug for the treatment of nematode infections caused by isolates of nematodes resistant to Ivermectin, Benzimidazole, Levamisole and Morantel.[17]

2.4. Nitrophenols

2.4.1. Definition- Structure

Still called halogenated phenols, it is a class of synthetic anthelmintic mainly represented by Nitroxinil. It has in its structure a phenol group substituted in ortho (2 and 2 'positions) with a nitro and a halogen and in para (4 position) by a nitrile function[13] (Figure 1).

2.4.2. Action mechanism

These are just like Salicylanilides, proton ionophores specifically decoupling the oxidative phosphorylation of mitochondria from the parasite's digestive cells without affecting those of the host. Enzymatic systems are disrupted, resulting in an energy depletion causing the death of the parasite.

2.4.3. Spectrum of action and indications

Nitroxinil has very marked anthelmintic properties:

1. With regard to the moat of the genus Fasciola (hepatica and gigantica ,
2. With regard to numerous hematophagous nematodes, parasites of ruminants

It is used in the treatment of gastro-intestinal fascioliasis and nematodoses in cattle and sheep (Table 1).[27]

2.5. Imidazothiazoles

2.5.1. Definition — structure

Imidazothiazoles are a class of compounds anthelmintics active against gastrointestinal strongyles in cattle and pigs, whether in adult or larval form.[17] These active principles have in their structure

animidazole nucleus attached to a thiazole nucleus, hence their name imidazothiazole. At present, two compounds are used therapeutically: Tetramisole, used in racemic form and levamisole, its laevorotatory isomer 10 times more active (Figure 1).[17]

2.5.2. Mechanism of action

These are cholinomimetics. They act selectively as agonists of nicotinic acetylcholine receptors (nAChRs) at the synapses of nematode muscle cells. They preferentially activate the 35pS channels (subtype L) and induce the opening of the non-specific ion channels permeable to Na^+ and Ca^{2+}.[28]Calcium entered into the sarcoplasmic reticulum via nAChRs also induces the opening of calcium channels dependent voltages (VACC). The calcium present in the sarcoplasmic reticulum produces either directly or by activation of ryanodine receptors (RyR) a membrane depolarization resulting in muscle contraction.[28]This results in severe and reversible spastic paralysis of the parasite which is then expelled from the host by peristalsis.

2.5.3. Spectrum of action and indications

Imidazothiazoles are active in gastrointestinal strongyloses in ruminants, pigs and rabbits. The efficacy is very good on Haemonchus, Trichostrongylus, Cooperia, Chabertia, adult and immature Oesophagostomum[6,17] (Table 1).

2.6. Tetrahydropyrimidines

2.6.1. Definition- structure

The tetrahydropyrimidine are a class of anthelmintics has wide spectrum of action. They possess the[1–6] nucleus, tetrahydropyrimidine methylated on nitrogen 1, and C^2-connected to a vinylthienyl or stryryl residue whose ethylenic chain is of trans configuration are available as tartrate or pamoate.[17]This class has three molecules, but only pyrantel pamoate is commonly used.

2.6.2. Mechanism of action

These are cholinergic agonists that bind to the nicotinic acetylcholine receptors of gastrointestinal nematodes. This fixation induces a change in post-synaptic membrane permeability causing muscle contraction, followed by marked spastic paralysis of worms.[6]

2.6.3. Spectrum of action and indications

Their spectrum of activity extends to gastrointestinal strongles and respiratory strangles[29]. They are indicated for treating gastrointestinal strongyloses, but they have minimal activity against immature forms and stopped larval stages (L4).[6]

3. Anthelminthics Recently Introduced

3.1. Aminoacetonitrile derivatives

3.1.1. Definition-structure

Aminoacetonitriles are a new class of synthetic anthelmintics. Their specificity lies in their effectiveness vis-à-vis strains resistant to other anthelmintics. The only representative currently used in veterinary therapy is Monepantel (Figure 1).[6]From the structural point of view, this amino acetonitrile comprises an asymmetric carbon at the level of acetonitrile, the four substituents of which are a nitrile function, a methyl group (5-cyano-2- (trifluoromethyl) phenoxy) methyl and (4-trifluoromethylthio) benzamide.

3.1.2. Mechanism of action

Monepantel would act on the nicotinic cholinergic receptor specific for nematodes of the DEG-3 subfamily. Monepantel does not activate monovalent cation channels itself, it substantially increases late currents after choline channel activation. Aminoacetonitriles are positive allosteric modulators of *H. contortus* DEG-3 receptors.[6]They cause a hyper contraction of the bodily muscles, which leads to spasmodic contractions of the anterior portion of the pharynx, to paralysis and then to the death of the parasite.[16,28]

3.1.3. Spectrum of action and indications

Monepantel has a broad spectrum of activity against gastrointestinal nematodes, sheep, including adults and L4 larvae of the most important species. The main characteristic of this molecule is its good efficacy against strains of nematodes resistant to benzimidazoles, levamisole, macrocyclic lactones or even against multiresistant strains.

These efficacy results are complemented by good tolerance and low toxicity for mammals.[16,28] In addition, Monepantel is considered non-toxic to the environment (soil microflora, aquatic organisms, manure organisms, vegetation, etc).

Monepantel is recommended for the treatment and control of gastrointestinal nematodoses in sheep, especially when they are resistant to one of the three classes of broad-spectrum anthelmintics.[28]

3.2. Spiroindoles

3.2.1. Definition-structure

The main representative of this class is Derquantel. It is a 2-desoxyparaherquamide, semi-synthetic analogue obtained by chemical reduction of paraherquamide, a fermentation product of *Penicillium simplicissimum.*[30]Derquantel is the first spiroindole anthelmintic that was marketed in 2010 in veterinary medicine in combination with a macrocyclic

Table 2: Biological targets for anthelmintic classes acting through ion channels[31,32]

Biological targets	Classes of anthelmintics	Species of nematode / genes found
Glutamate-dependent chloride channels (GluCl)	Macrocyclic lactones	C. elegans / glc-1, glc-2, glc-3, apr-14ba (gbr-2b), Apr-15 H. contortus / Hco-Glc-2b (HG4), HCO-glc-3b, HCO-April-14 b (HG3, GluCla3B), HCO-glc-5 (GluCla, HG5) Hco-Glc-6 b
Nicotinic Receptors of Acethylcholine (nAChR)	Imidazothiazoles	C. elegans / nAChR L-type: lev-1, lev-8, unc-29, unc-38, unc-63. n-type nAChR: acr-16
	Tetrahydropyrimidine	H. contortus / L nAChR Type: Hco-acr-8, Hco-yeast-1c, HCO-29, unc-d, HCO-unc-38, unc-HCO-63.
	Spiroindoles	A. suum / nAChR L-type: unc-29, unc-38. n-type nAChR: acr-26R
Cholinergic receptors	Amino-acetonitrile	C. elegans / acr-23, deg-3, des-2 H. contortus / Hco mptl-e-1, HCO-deg-3, HCO-deg-2
SLO-1 potassium channels and Latrophilin receptors	Cyclooctadepsipeptides	C. elegans / slo-1, lat-1 H. contortus / Hco-slo-1, Hco-lat-1 (Hc-110R)

lactone, abamectin (Startect®).

3.2.2. Mechanism of action

Three nicotinic receptors were identified in *Ascaris suum* **:** the subtype N (activated by nicotine), the subtype L (activated by levamisole and pyrantel) and the subtype B (activated by bephenium) respectively corresponding to 24pS, 35pS and 45pS channels.[30,33] Derquantel acts as a selective and competitive antagonist of nicotinic acetylcholine receptors by interfering with the 35pS (subtype L) and 45-pS (subtype B) channels leading to flaccid paralysis nematodes that are then expelled from the host.[6] The antagonist effect of Derquantel est plus important in sensitive receiver Pyrantel on the sensitive receiver Levamisole, the Derquantel also remains active on some resistant strains Levamisole.[28]

3.2.3. Spectrum of action and indications

Derquantel is active against L4 adults and immature forms of all major gastrointestinal nematodes, namely *Haemonchus contortus, Teladorsagia circumcincta, Trichostrongylus axi, Trichostrongylus colubriformis, Nematodirus spathiger,* etc. The association with Abamectin broadens its spectrum of activity and larval stages hypobiotiques.[28] This combination has demonstrated good efficacy against a range of mutant nematodes of variable resistance status and efficacy against resistant and multi-resistant nematodes.[34]

3.3. Cyclooctadepsipeptides

3.3.1. Definition- structure

Emodepside is the only representative of this family of cyclooctadepsipeptides currently available (Figure 1). It is a semi-synthetic compound of a derivative of fermentation product PF1022A of Mycelia sterilia mushroom.[35] He was introduced to therapy in 2001.[19]

3.3.2. Mechanism of action

Two modes of action for Emodepside have been described; firstly, binding to presynaptic G protein-coupled receptors (HC110-R) and secondly pre- and post-synaptic interactions with a Ca2 + activated K +ion channel (SLO-1).20,28 As a result, binding to latrophiline receptor and ion channel SLO-1 leads to inhibition of pharyngeal pumping, then occur atonic paralysis and death of the worm.[18]

3.3.3. Spectrum of action and indications

Emodepside is available in therapeutic combination with Praziquantel (a schistosomicide) in Profender. It is used as a spot-on in cats and tablet in dogs against the main gastrointestinal nematodes and cestodes. Its efficacy has also been demonstrated against some small strongyles (cyathostomes) in horses, against *Trichostrongylus colubriformis* and *Haemonchus contortus* in sheep and against *Dictyocaulus viviparus* in cattle. Due to its new dual mode of action, Emodepside is effective against nematodes resistant to classical anthelmintics.[36,37]

4. Ionic Channels As Potential Targets for New Anthelmintics

Many anthelmintic drugs used today act on the nervous system of nematodes (Table 2). Ionic channels as targets have certain advantages. Indeed, anthelmintics acting through this, quickly paralyze worms and fight effectively and quickly the infection. Thus, the macrocyclic lactones bind to an allosteric site of the glutamate-dependent chloride channels, either by directly activating the channel or by amplifying the effect of the neurotransmitter physiological,

glutamate.[31]

Many anthelmintics both old and new, including aminoacetonitrile derivatives, act as agonists of nicotinic acetylcholine receptors. Derquantel is an antagonist of these receptors. The Emodepside has multiple effects, affecting both a potassium channel and a receptor coupled to the pre-synaptic G protein.[31]

5. Conclusion

Veterinary helminths and their treatment are a socio-economic issue because they remain the main cause of economic losses in livestock farming. This situation persists for two main reasons. The first is the low level of veterinary coverage against helminths in small ruminants. The second reason is mainly related to the emergence of parasitic strains resistant to anthelmintic drugs, especially 2-carbamoyl-benzimidazoles. Indeed, despite their efficacy, these anthelmintics present several limitations in their practical use. Due to the elimination of some anthelmintics or their metabolites in milk, their use in small ruminant dairy species is limited. Only Febantel, Oxfendazole and Fenbendazole are used during lactation. In addition, some of these anthelmintics, namely macrocyclic lactones, are toxic to coprophagous beetles that are fertilizing agents in grassland fertilizers. Finally, due to the increasing appearance of helminth populations resistant to existing antiparasitic drugs, and in the search for new effective molecules with innovative mechanisms of action to allow a more durable control of this parasitism, nicotinic acetylcholine receptors may be selected as a preferred target for the development of new synthetic molecules.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Constable PD, Hinchcliff KW, Done SH, Gruenberg W. Veterinary Medicine A textbook of the diseases of cattle, horses, sheep, pigs and goats - two-volume set; 2016. p. 603–13.
2. Hotez PJ, Savioli L, Fenwick A. Neglected tropical diseases of the Middle East and North Africa: review of their prevalance, distribution, and opportunities for control. *PLoS Negl Trop Dis*. 2012;6(2):1475. doi:10.1371/journal.pntd.0001475.
3. Charlier J, Voort MVD, Kenyon F, Skuce P, Vercruysse J. Chasing helminths and their economic impact on farmed ruminants. *Trends in Parasitol*. 2014;7(30):361–8. doi:10.1016/j.pt.2014.04.009.
4. Kamuanga MJB, Somda J, Sanon Y. CSAO/OCDE. Livestock and regional market in the Sahel and West Africa; 2008. Available from: https://www.oecd.org/swac/publications/41848366.pdf.
5. Hoste H, Guitard JP, Pons JC. Pâturage mixte entre ovins et bovins : intérêts dans la gestion du parasitisme par les strongles gastro-intestinaux. *Alter-Agri*. 2003;61:20–23.
6. Lanusse CE, Alvarez LI, Lifschitz AL. Gaining Insights Into the Pharmacology of Anthelmintics Using Haemonchus contortus as a Model Nematode. *Adv Parasitol*. 2016;93:465–518. doi:10.1016/bs.apar.2016.02.014.
7. Getachew T, Dorchies P, Jacquiet P. Trends and challenges in the effective and sustainable control of Haemonchus contortus infection in sheep: review. *Parasite*. 2007;14(1):3–14. doi:10.1051/parasite/2007141003.
8. Taylor MA, Coop RL, Wall RL, Parasitology V. Veterinary Parasitology; 2013. p. 256.
9. Gordon HM. Phenothiazine as an anthelmintic. *Aus Vet J*. 1945;1:90–5.
10. Brown HD, Matzuk AR, Ilves IR, Peterson LH, Harris SA, Sarett LH, et al. Antiparasitic drugs IV. 2- (4'-Thiazolyl) -benzimidazole a new anthelmintic. *J Am Chem Soc*. 1961;83(7):1764–9.
11. Coles G, East JM, Jenkins SN. The mechanism of action of the anthelmintic levamisole. *Gen Pharmacol* . 1975;6(4):309–22.
12. Janssen M, Sipido VK. Antiparasitic salicylanilide derivatives. *United States Patent*. 1977;4:218.
13. Davis M, Rosenbaum J, Wright DE. Chemotherapy of fascioliasis. II. 4-Cyano-2-iodo-6-nitrophenol (nitroxynil) and related compounds. *J Sci Food Agric*. 1969;20(12):748–54.
14. Turner MJ, Schaeffer JM. Mode of action of ivermectin; 1989. p. 73–88.
15. Danis M, Lenoble DR. Medicine 2015 for tropical countries: ivermectin, an antiparasitic drug undeniable against filariasis. *Med Sci*. 2016;32(1):110–5. doi:10.1051/medsci/20163201018.
16. Kaminsky R, Gauvry N, Schorderet WS, Skripsky T, Bouvier J, Wenger A, et al. Identification of the amino-acetonitrile derivative monepantel (AAD 1566) as a new anthelmintic drug development candidate. *Parasitol Res*. 2008;103(4):931–40. doi:10.1007/s00436-008-1080-7.
17. Noireau C. Therapeutic chemistry. vol. 2; 1998. p. 544.
18. Ed L. Dictionary of Veterinary Medicines and animal health products (DMV); 2016. p. 2531.
19. Thomas SP. Recent data on resistance to anthelmintics in the gastrointestinal strongyles of ruminants. . *J Vet Intern Med*. 2003;20(2):100.
20. Robertson AP, Buxton SK, Puttachary S, Williamson SM, Wolstenholme AJ, Neveu C, et al. Antinematodal Drugs - Modes of Action and Resistance: And Worms Will Not Come to Thee (Shakespeare: Cymbeline : IV, ii). *Parasitic Helminths: Targets, Screens, Drugs Vaccines*. 2012;p. 233–82. doi:10.1002/9783527652969.ch14.
21. Campbell WC. Benzimidazoles: veterinary uses. *Parasitol Today*. 1990;6(4):130–3. doi:10.1016/0169-4758(90)90231-r.
22. Shoop WL, Mrozik H, Fisher MH. Structure and activity of avermectins and milbemycins in animal health. *Vet Parasitol*. 1995;59(2):139–56. doi:10.1016/0304-4017(94)00743-v.
23. Prichard R, Ménez C. Moxidectin and the avermectins: consanguinity but not identity. *Int J Parasitol Drugs Drug Resist*. 2012;14(2):134–53. doi:10.1016/j.ijpddr.2012.04.001.
24. Arena JP, Liu K, Mrozik H, Frazier EG, Cully DF. The mechanism of action of avermectins in Caenorhabditis elegans : correlation between activation of sensitive chloride current, membrane binding, and biological activity. *J Parasitol*. 1995;81(2):286–94.
25. Swan GE. The pharmacology of halogenated salicylanilides and their anthelmintic use in animals. *JI S Afr Vet Assoc Ass*. 1999;70(2):61–70.
26. Blackhall WJ, Liu HY, Xu M, Prichard RK, Beech RN. Selection at a glycoprotein gene in ivermectin and moxidectin-selected strains of Haemonchus contortus. *Mol Biochem Parasitol*. 1998;95(2):193–201. doi:10.1016/s0166-6851(98)00087-5.
27. Makkar MS. Some pharmacological studies on nitroxynil (4-cyano-2-iodo-6-nitrophenol). *Indian J Anim Res*. 1974;8(2):81–3.
28. Kotze AC, Hunt PW, Skuce P, S-Himmelstjerna GV, Martin RJ, Sager H. Recent advances in candidate-gene and whole-genome approaches to the discovery of anthelmintic resistance markers and the description of drug / receptor interactions. *Int J Parasitol Drugs Drug Resist*. 2014;4(3):164–84. doi:10.1016/j.ijpddr.2014.07.007.

29. Chartier C, Pors I, Benoit C. Efficacy of pyrantel tartrate against experimental infections with Haemonchus contortus , Teladorsagia circumcincta and Trichostrongylus colubriformis in goats. *Vet Parasitol*. 1995;59(1):69–73. doi:10.1016/0304-4017(94)00737-w.
30. Woods DJ, Maeder SJ, Robertson AP, Martin RJ, Geary TG. Discovery, Mode of Action, and Commercialization of Derquantel. *Parasitic Helminths: Targets, Screens, Drugs Vaccin*. 2012;p. 297–307.
31. Wolstenholme AJ. Ion channels and receptor as targets for the control of parasitic nematodes. *Int J Parasitol Drugs Drug Resist*. 2011;1(1):2–13. doi:10.1016/j.ijpddr.2011.09.003.
32. Dye LH, Joyner M, O'connor V. Nicotinic acetylcholine receptors: A comparison of the nAChRs of Caenorhabditis elegans and parasitic nematodes. *Parasitol Int*. 2013;62(6):606–21. doi:10.1016/j.parint.2013.03.004.
33. Robertson AP, Trailovic SM, Burns TA, Thompson DP, Geary TG. Paraherquamide and 2-deoxy-paraherquamide distinguish cholinergic receptor subtypes in Ascaris muscle. *J Pharmacol Exp Ther*. 2002;302(3):853–60. doi:10.1124/jpet.102.034272.
34. Little PR, Hodges A, Maeder SJ, Wirtherle NC, Nicholas DR, Cox GG. Efficacy of the oral formulation of derquantel-abamectin against the adult and larval stages of nematodes in sheep, including anthelmintic-resistant strains. *Vet Parasitol*. 2011;181(2-4):180–93. doi:10.1016/j.vetpar.2011.05.008.
35. Sasaki T, Takagi M, Yaguchi T, Miyadoh S, Okada T, Koyama M. A new anthelmintic cyclodepsipeptide PF1022A. *J Antibio*. 1992;45(5):692–7. doi:10.7164/antibiotics.45.692.
36. Himmelstjerna VS, Harder G, Sangster A, Coles NC. Efficacy of two cyclooctadepsipeptides, PF1022A and emodepside, against anthelmintic-resistant nematodes in sheep and cattle. *Parasitology*. 2005;130(3):343–50. doi:10.1017/s0031182004006523.
37. Lees K, Sluder A, Shannan N, Hammerland L, Sattelle D. Ligand-Gated Ion Channels as Targets for Anthelmintic Drugs: Past, Current, and Future Perspectives. *Parasitic Helminths: Targets, Screens, Drugs Vaccines*. 2012;6(2):3–21.

Author biography

Deto UJ-P N'guessan, Assistant Professor

Cite this article: UJ-P N'guessan D, Coulibaly S, Ouattara M. Pharmacotherapy of gastrointestinal strongylosis of small ruminants: An update. *Int J Pharm Chem Anal* 2021;8(4):159-166.