

When anthelmintics can cause illness and death.

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ABSTRACT

The role of helminths in small stock production, and hence the optimal use of anthelmintics to manage helminth infections, has received much attention. Over time, newer and more effective anthelmintics have been produced that controlled worms effectively for decades, but almost total reliance on treatment was not sustainable. The indiscriminate use of these drugs has in turn led to the development of widespread anthelmintic resistance in the helminth population. Although anthelmintic resistance is a major problem in small ruminant farming, it is often caused by underdosing of products by farmers and farm workers through incorrect weight estimation of the animals. The converse of this is also true and thus overdosing can have adverse effects and even result in death. These adverse effects of overdosing anthelmintics are discussed.

Key words: Sheep, ovine, anthelmintics, adverse effects, toxicity

INTRODUCTION

The most important worm in the summer rainfall areas of Southern Africa is *Haemonchus contortus*. The importance of the FAMACHA[®] system in controlling this parasite has been comprehensively reviewed and has not only been tested in Southern Africa but also in many countries including North America, Brazil, the Caribbean, and Europe. Time and again it has proven to be an effective way of assessing whether or not animals are able to cope unaided with high levels of *Haemonchus*. However, there are other parasites that cause losses and for these the Five Point Check[®] has proven to be useful in determining with safety which animal to leave untreated.

Many farmers are aware of the consequences of incorrect dosing leading to multiple anthelmintic resistance, however, not many are aware of the other potential problems associated with the uninformed use of anthelmintics. It is important to determine which product to use for which parasite and under which circumstances. It is also important to obtain an accurate weight before dosing animals to avoid adverse reactions to these anthelmintics.

The majority of anthelmintics have wide safety margins as they are selected for specifically targeting an area in the helminth's lifecycle, for example, those where the effect is based on antimitotic effects have some effect on the host species such as teratology or embryotoxicity. Most compounds that are active against flukes, as well as levamisole, do not have as wide a safety index. Other drugs such as tetrahydropyrimidines have a high safety margin due to their low absorption from the

gut. The absorption can be increased where there is gut damage however, and so it is important to take note when treating animals suffering from other illnesses.

THE MAJOR ANTHELMINTIC GROUPS

Anthelmintics in South Africa are grouped according to the mode of action of the active ingredients. The group number that a particular drug belongs to is displayed in a circle on the top right hand side corner of the label of the product. It is important to inform farmers of this so that they can use different groups if they are trying to dose for different worms to avoid overdosing from a specific group.

1) Macrocyclic Lactones

This drug group consists of avermectins (ivermectin, abamectin, doramectin, eprinomectin, selamectin) and milbemycins (milbemycin oxime, moxidectin). The macrocyclic lactones are used to treat both internal and external parasites and therefore there is a risk of overdose if using the same group to treat for worms and for mites for example. This is also the reason that there is widespread anthelmintic resistance to this group especially with *Haemonchus contortus*. The residence time of the drug when administered by subcutaneous injection depends on body condition score (BCS) and hence fat reserves, as the product is taken up by the fat cells and released slowly into the blood stream.

Cattle treated with 1.0mg/kg showed neurotoxicity and severe toxicosis with 2 to 8mg/kg. Sheep given a 3x overdose did not show adverse effects. Reported cases of toxicity are usually due to administration errors such as administering intra-

muscularly or intra-venous and repeated unintended treatment due to poor animal identification.

In thin or emaciated animals there will not be a slower release and more of the drug is released into the blood stream at one time than in animals that have fat reserves. Young animals do not have a very well developed blood-brain barrier and thus are more prone to adverse effects. Goats tend to deposit fat abdominally and so have less of a subcutaneous fat reserve. Oral dosing will be absorbed quicker into the blood. Therefore this group of drugs must be used with caution in young or thin animals and goats.

There is no antidote available for treatment.

2) Benzimidazoles

Mebendazole, flubendazole, fenbendazole, oxfenbendazole, oxibendazole, albendazole, albendazolesulfoxide, thiabendazole, thiophanate, febantel, netobimin and triclabendazole belong to the benzimidazole group. These anthelmintics are mostly used for roundworms although albendazole, netobimin and triclabendazole are effective against flukes as well. Triclabendazole is not used for roundworms. This group has a relatively high safety margin and therefore toxicosis is rare, however, they have teratogenic effects and therefore should not be used in pregnant animals. There is no antidote.

3) Imidazothiazoles

Tetramisole namely the L-isomer levamisole is used for roundworms. A 4x overdose causes toxicosis and even fatalities due to respiratory failure. Levamisole decreases the efficacy of phenylbutazone (non-steroidal anti-inflammatory) which is no longer

registered for use in food producing animals. It should also not be administered with the same needle as neomycin, tetracyclines and sulphonamides.

There is no antidote but Atropine may be tried in treatment protocols.

4) Salicylanilides

Closantel, niclosamide, oxyclozanide and rafoxinide belong to this group. Used mainly for flukes and nasal bot and some use for roundworms. The safety margin after oral administration is very low and therefore it is important to determine accurate weights before dosing. For its prolonged effect, the drug is bound to albumin. Thus if the animal is anaemic, it will be more susceptible to toxic effects. Anaemic animals should rather be treated with drugs from other groups. There is no antidote.

5) Substituted Phenols

Nitroxylnil belongs to this group. It is used against nematodes, flukes and as a double dose can be used to treat parafilaria. Three time an overdose can cause fatalities in cattle. There is no antidote.

6) Sulphonamides

Clorsulon falls into this group and is mainly used in combination with ivermectin. Clorsulon has a very high safety margin and is well tolerated by sheep, goats and cattle. It is used mainly for flukes.

7) Organophosphates

These include Dichlorphos, Trichlorphon, Haloxon, Naphthelphos and Crufomate.

Trichlorfon is used in sheep and goats. These were originally developed as pesticides and later as anthelmintics. Organophosphates accumulate in the environment and have a very low safety margin as a two times overdose is toxic. Atropine sulphate (1mg/kg) and 2 PAM (pralidoxime chloride) (2-5mg/kg) can be used for treatment as well as administering activated charcoal if dosed orally. It is important to remember that combining organophosphates with some other drugs such as synthetic pyrethroids can increase the toxicity of the synthetic pyrethroids even if administered at the therapeutic dose.

There is another aspect to organophosphate toxicity known as organophosphate-induced intermediate syndrome (can be caused by trichlorphon) and clinical signs include generalized weakness or paralysis, ptosis and diplopia. These clinical signs may last for days or even weeks and needs to be seen as a separate clinical entity from the usually acute toxicity and delayed neuropathy.

8) Isoquinolones

Praziquantel is used for the treatment of tapeworms. It has a very high safety margin of 40 times the therapeutic dose. There is no antidote.

9) Tetrahydropyrimidines/combinations/other

Tetrahydropyrimidines (pyrantel and morantel) is often used in combination with ivermectin or febantel. It has a relatively high safety margin, however, the mechanism of action is the same as the organophosphates and therefore atropine can be used to treat toxicities.

Amino-acetonitrile derivatives (monepantel) is mainly used against *Haemonchus* and has a very high safety index. There have been no reports of adverse reactions however, it may lead to an increase in the weight of the thymus, thyroid and adrenals and cause liver damage.

10) Spiroindoles

Derquantel (used in combination with abamectin) and is effective against roundworms. Adverse reactions are unknown as it is only used in combination with macrocyclic lactones. Refer to macrocyclic lactones.

ADVERSE EFFECTS OF THE MAJOR ANTHELMINTIC GROUPS

The table that follows serves as a guide for farmers and consultants to determine the best product to use and which to avoid in pregnant, young or thin or other at risk animals as well as clinical signs to look out for if an overdose is suspected.

See appendix A

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APPENDIX A

TABLE 1: Adverse effects of the major anthelmintic groups

DRUG GROUP	EFFECTS	USE	ADVERSE EFFECTS	PRECAUTIONS
1	<p><u>Macrocyclic Lactones</u></p> <ul style="list-style-type: none"> • Ivermectin • Abamectin • Doramectin • Eprinomectin • Selamectin • Milbemycin • Oxime • Moxidectin 	<ul style="list-style-type: none"> • Broad spectrum internal & external parasites 	<ul style="list-style-type: none"> • Ataxia • Hypermetria • Disorientation • Hyperesthesia • Tremor • Mydriasis (Myosis in cattle) • Recumbency • Depression • Blindness • Coma 	<ul style="list-style-type: none"> • Do not use in young or emaciated animals • Use with caution in goats. • Can cause death due to larval embolism when treating heart worm in cats and dogs or lungworm in cattle.
2	<p><u>Benzimidazoles</u></p> <ul style="list-style-type: none"> • Mebendazole[□] • Flubendazole • Fenbendazole[○] • Oxfendazole • Oxibendazole • Albendazole * • Albendazolesulfoxide • Triclabendazole • Netobimin * • Thiophanate • Febantel • Thiabendazole 	<ul style="list-style-type: none"> • Broad spectrum of nematodes (roundworms) <p>* Active against flukes</p>	<ul style="list-style-type: none"> • Teratogenic • Affects liver, testes and gastro-intestinal tract. • Lethargy appetite • Intestinal cramps • Nausea • Diarrhoea • Vomition • Dizziness • Convulsions • Sleeplessness 	<ul style="list-style-type: none"> □ Do not use in pregnant animals except for mebendazole ○ Can cause allergic reaction due to sudden death of worms
3	<p><u>Imidazothiazoles</u></p> <ul style="list-style-type: none"> • Levamisole 	<ul style="list-style-type: none"> • Roundworms 	<ul style="list-style-type: none"> • Depression • Restlessness • Hypersalivation • Vomition • Colic • Diarrhoea • Bradycardia • Collapse • Dyspnoea • Tachypnoea • Miosis • Spasms • Cramps • Trembling • Death • Painful swellings at injection site <p><u>Goats:</u></p> <ul style="list-style-type: none"> • Lacrimation • Miosis • Hiccups • Hyperactivity 	<ul style="list-style-type: none"> • Levamisole administered with chloramphenicol causes fatalities. • Levamisole enhances the effects of noradrenalin, angiotensin, acetylcholine. • Levamisole enhances the toxicity of organophosphates, carbamates, morantel, pyrantel and neostigmine. • Avoid using in sick/weak animals and should not be used after vaccination, dehorning or castrations.

4	<u>Salicylanilides</u> <ul style="list-style-type: none"> Closantel Nicosomide Oxyclozanide 	<ul style="list-style-type: none"> Fasciolasp <i>Haemonchusspp</i> <i>Oestrus ovis</i> 	<ul style="list-style-type: none"> Depression Colic Diarrhoea Opisthotonus Nystagmus Mydriasis Irreversible blindness Ataxia Inappetance 	<ul style="list-style-type: none"> Use with caution in lambs
5	<u>Substituted Phenols</u> <ul style="list-style-type: none"> Nitroxynil 	<ul style="list-style-type: none"> Nematodes Flukes Parafilaria 	<ul style="list-style-type: none"> Swelling and skin reactions at injection site. Tachycardia Hyperventilation Fever Increased excitability 	<ul style="list-style-type: none"> Oral administration results in rumen microbes breaking down in product. Therefore administration via injection is preferred.
6	<u>Sulphonamides</u> <ul style="list-style-type: none"> Clorsulon 	<ul style="list-style-type: none"> Flukes 	<ul style="list-style-type: none"> Transient swelling at injection site. 	
7	<u>Organophosphates</u> <ul style="list-style-type: none"> Trichlorfon 	<ul style="list-style-type: none"> Internal and external parasites (broad spectrum) 	<p>Muscarinic signs:</p> <ul style="list-style-type: none"> Bradycardia Dyspnoea Diarrhoea Vomition Colic Hypersalivation <p>Nicotinic:</p> <ul style="list-style-type: none"> Muscle fasciculation and weakness <p>Central:</p> <ul style="list-style-type: none"> Ataxia Nervousness Seizures Depression 	<ul style="list-style-type: none"> Do not use for internal parasites if already applied for external parasites and <i>vice versa</i>.
8	<u>Isoquinolones</u> <ul style="list-style-type: none"> Praziquantel 	<ul style="list-style-type: none"> Tapeworm 	<ul style="list-style-type: none"> Salivation Depression Vomition Ataxia 	<ul style="list-style-type: none"> Pain at injection site. Therefore do not give >3ml per site.
9	<u>Tetahydropyrimidines</u> <ul style="list-style-type: none"> Pyrantel Morantel <u>Amino-acetonitrile derivatives</u> <ul style="list-style-type: none"> Monepantel 	<ul style="list-style-type: none"> Nematodes <i>Haemonchus</i> 	<ul style="list-style-type: none"> Ataxia Excitation Convulsions Tremors Vomition Diarrhoea Hyperhidrosis (excessive sweating) Salivation Tachycardia None found 	<ul style="list-style-type: none"> Pyrantel must not be given to weak or sick animals. Damaged gastro-intestinal tract can increase toxicity due to increased absorption. Do not administer with levamisole as it has the same mechanism of action. None recorded
10	<u>Spiroinoles</u> Derquantel	<ul style="list-style-type: none"> Nematodes 	<ul style="list-style-type: none"> Unknown Refer to Macrocylic Lactones 	<ul style="list-style-type: none"> Combined with abamectin