European Platform for the Responsible Use of Medicines in Animals

EPRUMA best-practice framework on the use of anthelmintics in food-producing animals

INTRODUCTION

EPRUMA has been established to promote the responsible use of medicines in animals (www.epruma.eu) and spread information on best practices[1] to tackle challenges, which may compromise the health of animals and people.

Helminth infections of animals, such as ruminants (cattle, sheep and goats), poultry and equine, are usually subclinical and may result in large economic losses. If left untreated, they can cause serious suffering or even death of the infected animals. Therefore, responsible use of effective anthelmintics is essential to safeguard animal health, welfare and production. However, anthelmintic resistant gastrointestinal worm populations in food-producing animals are already a challenge for farmers, horse owners and veterinarians worldwide.

EPRUMA partners have recognised the emerging risk of anthelmintic resistance and agree that it is time to take action to ensure the responsible use of veterinary anthelmintics in food-producing animals.

GENERAL INFORMATION ABOUT HELMINTHS

Helminths are multicellular invertebrates characterised by flat or round bodies. The three major groups of parasitic helminths are

- nematodes (rounded body)
- cestodes (segmented flat worms = tapeworms)
- trematodes (non-segmented flat worms = flukes).

Depending on their specific life cycle and life cycle stage, they target different organs in animal or human bodies, *e.g.* gastrointestinal tract, liver, lungs or skin.

Infections by helminths are common in most animals and may also cause zoonotic diseases in humans. The cycle of transmission varies with the species of worm; it may involve ingestion of different stages (egg, larvae), penetration by larvae, ingestion of intermediate hosts, or transmission by arthropod vectors (insects or acarians).

Usually, there is a balance between helminth infestation and the immune system of the host. As a result, clinical symptoms, such as loss of weight, loss of productivity, increased feed conversion rate

[1] Best-practice framework for the use of antibiotics in food-producing animals in the EU and Best-practice framework for the use of antimicrobials in food-producing animals in the EU - Reaching for the next level

or mortality, are not always present. Only animals that have not yet developed their immunity or have their immunity against worms compromised *e.g*. young or sick animals, as well as those which are heavily infected with parasites, would show symptoms of disease.

DIAGNOSIS

Farmers play an essential role by monitoring the health of animals under their care on an ongoing basis. The animals are thus observed regularly by farmers and veterinarians so as to ensure that the first signs of disease are detected and that appropriate action is taken at the earliest opportunity.

As with any other health condition, the first step to take when disease occurs is to ensure that the veterinarian examines the animal(s) and the circumstances in which they are kept.

Diagnosis of helminthic diseases can be done based on the clinical examination and the collection of faecal samples for testing to detect a parasite infection. Some helminth infections can also be detected with serological methods from blood or milk samples or post-mortem examination. Feedback from abattoirs concerning parasite infection (e.g. liver flukes) from slaughtered animals are useful information as well.

Proper diagnosis is necessary to allow for both a targeted treatment, and also for holistic management of the herd/flock/farm via a proper health plan that can lead to the control of parasite populations in order to minimise the risk of clinical disease.

TREATMENT OF HELMINTIC INFECTIONS

The use of the proper anthelmintic can either control the level of parasitic infections, thus avoiding clinical signs and economic impact, or treat sick animal(s).

An anthelmintic is an active pharmaceutical substance that kills parasitic worms by many different modes of actions depending on the groups of active ingredients. They are commonly called dewormers or ‘wormers’, but can also be called parasiticides, endoparasiticides, endectocides, nematodicides, cestodicides, trematodicides, flukicides or antiparasitics.

Anthelmintics are divided into classes based on similar chemical structure and mode of action. Currently available broad-spectrum anthelmintics belong to five different chemical groups:

1) benzimidazoles (such as mebendazole, flubendazole, fenbendazole, oxfendazole, oxibendazole, albendazole, albendazole sulfoxide, thiabendazole, thiophanate, febantel, netobimin and triclabendazole),
2) imidazothiazoles (mainly levamisole),
3) macrocyclic lactones (such as ivermectin, eprinomectin, abamectin, doramectin and moxidectin),
4) amino-acetonitrile derivatives (such as monepantel),
5) spiroindoles (such as derquantel).

Anthelmintics are not antibiotics. Different anthelmintic products of the above groups are authorised in Europe for use in food-producing animals (*i.e.* bovine, small ruminants, poultry and laying hens,

swine) and horses. They can be used for the treatment of sick animals or animals at risk of getting sick following a veterinary prescription by a veterinarian[2].

Anthelmintic products can be administered by different ways, *i.e*. orally (via in-feed, boluses, 'drenches'), by injection or topically ('pour on'). Each authorised product has a withdrawal period stated on its label that must be respected to ensure consumer safety. The withdrawal period varies according to the target and category of animal species, the animal product, *e.g.* milk, meat, eggs, *etc.* and the pharmacological properties of the product. National and EU monitoring of residues of veterinary medicines in animals and food stuffs confirm that these withdrawal periods are well adhered to.

ANTHELMINTIC RESISTANCE: IMPACT AND RESPONSE

Anthelmintic Resistance (AHR) is the genetic ability of worms/helminths to survive the standard recommended dose of an anthelmintic product, which would normally be effective to kill the majority (i.e. ≤90%[3]) of the targeted parasites.

Anthelmintic resistance has been present for many years, especially in gastrointestinal nematodes of ruminants and horses. As a result, in certain regions some of the anthelmintic products used to treat those conditions may be ineffective due to increase of helminths' tolerance or resistance.

Considering the relevance these conditions can have on the animal health, animal welfare and productivity, it is of utmost importance to take action to ensure that anthelmintic products will continue to be effective in the future and that innovation delivers new molecules with new mode of actions.

RECOMMENDATIONS FOR BEST PRACTICE

EPRUMA has extensively worked on antibiotic resistance and presented a set of integrated measures which represent best practices against antibiotic resistance, and to preserve antibiotic efficacy. Even if a completely different and unrelated topic, EPRUMA, based on this background, is now proposing to analyse the risk of anthelmintic resistance.

EPRUMA recommendations:

- Ensuring animal health
  - ✓ Good management practice[1] is fundamental to ensure animal health, which is a precondition for animal welfare and the maintenance of good productivity. An open communication between the farmer and experts including veterinarians is essential to achieve optimal animal health. Adequate management of the pasture according to weather conditions during the grazing season, adequate housing/climate, adequate nutrition per species and production type, as well as selection of robust animals are key in ensuring a good health status.
  - ✓ Biosecurity measures and management procedures, e.g. grazing conditions, can minimise the risk of new infections. Prevent the introduction of worm problems by quarantining and treating imported animals in accordance with advice from a veterinarian.

[2] Or a veterinary prescription according to national legislation.

[3] Source: VICH guideline 7 on the efficacy of anthelmintics: general requirements (page 4)

- ✓ Developing an overall farm health plan with the advice from your veterinarian and other professional consultants, is essential to ensure proper animal vaccination and a deworming strategy on the farm based on targeted selective treatments (TST)[4] including a full grazing management programme, where appropriate, to reduce the need for treatment.
- ✓ Maintenance of a population of parasites in refugia is a strategy aiming to slow the rate of selection of anthelmintic resistance. Parasites in refugia are those that are not exposed to an anthelmintic, including those present as free-living stages in the environment, in untreated individuals, and any lifecycle stages in the host that are refractory to anthelmintic treatment. Best farm practices and pasture management can maintain refugia, also called 'susceptible reservoir', which could be an important tool to slow the selection process of anthelmintic resistance in certain parasitic species.

- ➢ Diagnosing and treating disease - Ensure a responsible use of anthelmintics
  - ✓ Use clinical examination of the animal(s) together with other means of diagnosis, such as analysis of faecal samples or serology (bulk-milk or blood), to help determine the need to treat and allow for the prescription of the appropriate medicine.
  - ✓ Ensure effective treatment by taking care to correctly dose the animals by use of determined bodyweights, correct administration and calibration of the dosing device.
  - ✓ Follow the prescription and respect the withdrawal period.
  - ✓ Try to avoid frequent and repeated use of anthelmintics of the same class over an extended period. Preserve susceptible worms on the farm (*in refugia* population) by conducting part-flock treatments and targeted selective treatments.
  - ✓ Some countries already have guidelines for the responsible use of anthelmintics[5]. Those guidelines should be followed when available, and knowledge and information sharing between countries should be encouraged.

- ➢ Monitoring of anthelmintic resistance
  - ✓ Investigate where feasible, and report suspected cases of resistance or lack of efficacy to a particular anthelmintic (notify pharmacovigilance system as appropriate). Ensure effective treatment by using anthelmintics belonging to another pharmacological class.
  - ✓ Use any available *in-vivo* and *in-vitro* methods to regularly assess the efficacy of anthelmintics where possible.

- ➢ Promote and encourage the availability of appropriate authorised anthelmintics for all species in all European countries.

[4] Targeted Selective Treatment (TST) refer to treatment of only a proportion of the flock at a time, based on their productive performance or the outcome of diagnostic tests, leaving the unaffected/less affected animals untreated. TST has been proposed as a novel and sustainable control strategy to prevent the development of anthelmintic resistance, as it will maintain populations of nematodes in refugia (i.e. pre-parasitic stages in the environment unexposed to anthelmintics).

[5] For the UK: http://www.ruma.org.uk/antiparasitics/; , www.SCOPS.org.uk; www.cattleparasites.org.uk
For Spain Vetresponsable: http://www.vetresponsable.es/vet-responsable/documentos/uso-prudente-de-antihelminticos_295_1_ap.html
For Germany: http://www.weide-parasiten.de/

- Need for further research on best practices, innovation for new modes of actions and alternatives, such as vaccination
  - ✓ Mechanisms of anthelmintic resistance are to a large extent unknown, but are likely to be related to the molecule classes, modes of action and detoxification. Although various *in-vivo* and *in-vitro* methods have been developed to assess the efficacy of anthelmintics and confirm or not a suspicion of resistance, the last remains still a difficult task.
  - ✓ The animal's immune response to helminthic infections does not follow the same pattern as immune response to bacterial infections. Vaccination approaches against helminths have not yet been successful due to the complexity of invertebrates.
  - ✓ More research is necessary on understanding the mechanisms for the development of anthelmintic resistance on new, easy-to-use, reliable and cost-effective treatment options, on diagnostic tools and on alternatives, such as vaccination.

CONCLUSION

Safeguarding existing anthelmintics depends on the implementation of good management practices which ensure good biosecurity measures and farm environment to limit infection pressure, an adequate nutrition and the selection of robust animals.

To keep them effective, anthelmintics should be used responsibly, after careful consideration and under veterinary oversight, and in the context of sustainable, integrated control programmes.

The use of the proper anthelmintic can restore health of the animal(s), while proper management can prevent the spreading of the infection. Use of diagnostic testing should be encouraged to both identify the parasite and select the appropriate treatment to be prescribed by the veterinarian.

As with antibiotic or insecticidal resistance, anthelmintic resistance needs the commitment and coordinated efforts of all involved stakeholders for further research on better understanding the resistance mechanisms, as well as on best practices, innovation for new modes of action and on alternatives, such as vaccination.

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