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# Endectocides in goats: Pharmacology, efficacy and use conditions in the context of anthelmintics resistance☆

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ABSTRACT

Endectocides (avermectins/mibemycins) are today one of the most important anthelmintic families for the control in livestock nematodes and their use is increasing in goats because of the high frequency of benzimidazole resistance. Goat has specific pharmacological parameters for endectocides compared to sheep or cattle (absorption and elimination). The behaviour of the drug in the organism, represented by pharmacokinetic parameters, is affected through several ways including the route of administration and drug formulation, and the host animal (nutrition, parasitism, physiological status, amount of fat tissue). For each species, the determination of specific dose rates is needed to insure an optimal activity against nematodes (particularly those inhabiting the small intestine). This scientific knowledge is a prerequisite to a better use of the different anthelmintic families in goats. An important objective in the chemical control of nematodes is to define the best deworming practices that reduce the risk of nematode resistance occurrence through a decrease of selection pressure on nematode populations. The main points of a rational use of anthelmintics include the dose rate, the route of administration, the annual frequency and the period of treatment, the alternative use of families and the selective treatment of high excreting animals.



## 1. Introduction

Dairy goat is probably the most sensitive domestic ruminant to parasitism by nematodes. The origin of this sensitivity compared to cattle and sheep may be physiological and/or nutrition or related to a process of natural selection having slowly operated as a result of feeding behaviour. Goats are classified as browsers, reducing the exposition of animals to parasites (Hoste et al., 2010). This low resistance to parasites is expressed especially in primiparous goats and those with high milk production and exposes the animals to parasitic infections that can lead to a deficit of milk production by nearly 20% (Chartier et al., 2000; Hoste et al., 2001). Today, anthelmintic drugs are now the main, if not the only tool to control nematodes in dairy goats.

Their use by farmers has been recently described by Hoste et al. (2000), all farms using anthelmintics at a rate of nearly 3 treatments per year, except in organic farms. The treatments were collective (whole herd), using essentially benzimidazoles (>80%), at doses defined for sheep in nearly 50% of cases and without alternating anthelmintic family from one year to another. Such practice leads in most of the cases to under-dosing and to lower drug efficacy in goats, with significant risk for selection of nematode resistant to anthelmintics. Previous studies show that the

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prevalence of resistance of goat nematodes to anthelmintic in France varies between 70 and 100% of farms for the benzimidazoles, which have been the most used so far, whereas for the moment no resistance have been reported for the other two families, levamisole and pyrantel and avermectin–milbemycin (endectocides) (Chartier et al., 2001; Paraud et al., 2010). However, endectocides-resistant nematodes in goats have been reported in other parts of the world (Australia, South Africa). In livestock including goats, there is an urgent need to improve the management of endectocides-based therapeutic, because of their remarkable broad-spectrum activity, safety profile and ease of administration.

The notion of "limited resources of anthelmintic" that we need to protect seems today fundamental (Williams, 1997). This concern is coupled with the preoccupation of presence of residues in the animal products and with an impact on the environment (Bounias, 2000). A better knowledge of the behaviour of the drug in the host organism and of the factors that controls this behaviour is essential to optimize of the usage of anthelmintics. Indeed, there is clear relation between the drug concentration in the body and its antiparasitic efficacy. Finally, any information provided related to the drug pharmacokinetic can be applied in the daily practice for short term antiparasitic therapeutic control, but, also, in the longer term to define strategy to control parasites and to limit the development of the resistances to anthelmintics. It is necessary to specify that no endectocide are authorized for usage in goat and that the use of these molecules is made under the responsibility of the clinician.

## 2. Pharmacology of endectocides in goats

Anthelmintic activity is related to two main aspects:

- the specific action of the drug on the target parasite and it paralysed it by interfering with the transmission of the nervous signal controlled by the glutamate;
- the effective presence of the active drug on the site of action in term of concentration and of duration (the minimal active concentration is not established, and varies according to the target parasite) (Baggot and McKellar, 1994).
- it is generally accepted that the antiparasitic effect is more strictly connected to the exposure of the animal level to the drug measured by the area under the plasma concentration versus time curve (AUC) that to the administered dose (Rowland and Tozer, 1995). Indeed, the dose is a compulsory variable that is translated in the body in a profile of concentration of the active molecule which is modulated by the physiological and metabolic properties (bioavailability, distribution, clearance) of the animal. From then on, the profile of the plasma concentrations is an explanatory variable much more relevant than the dose.

The application of these two concepts supposes the relevance of the plasma concentration to reflect the concentrations at the level of the site of action. It has been established a narrow correlation between the concentrations in plasma and the concentrations measured at the level of sites of action where parasites locate such as the skin or the abomasal mucus (Fig. 1) (Lifschitz et al., 1999). Indeed, not only the profiles are parallel, but also the concentrations in target tissues are superior to those observed in the plasma. Similar results were obtained for doramectin and ivermectin in sheep and in goats (Baggot and McKellar, 1994; Lespine et al., 2005). We can consider that in the case of endectocides, the plasma parameters are relevant parameters to predict the anthelmintics activity in the site of drug action.

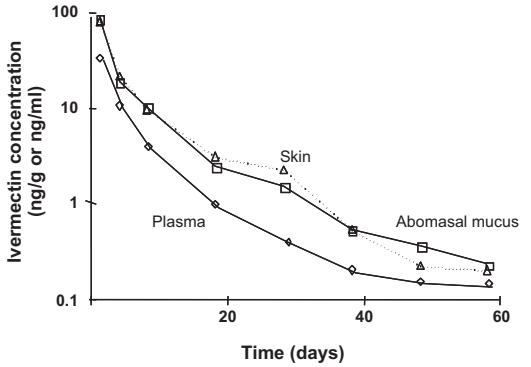


**Fig. 1.** Correlation between ivermectin concentration in plasma and in target tissues in cattle after subcutaneous administration of 0.2 mg/kg ivermectin (Lifschitz et al., 1999).

There are several factors involved in therapeutic efficacy and related to the pharmacokinetic evaluation:

- the formulation and the active drug;
- the route of administration;
- the host and its physiopathology.

### 2.1. Formulation and compound

The comparison of the pharmacokinetic profiles of two endectocides, doramectin and moxidectin, administered by subcutaneous route at the dose of 0.2 mg/kg in adult goats, revealed clear differences in the behaviour of the two drugs, which confirms previous observation in other species (Escudero et al., 1999). When compared with ivermectin, different molecule of endectocides administrated at a same route and dose in goat lead to different levels of concentration and subsequently to different exposure of the host to the drug (Fig. 2). This is in agreement with the different physicochemical properties of each molecule or formulations that lead to specific behaviour. Moxidectin is more lipophilic than the two others and remains longer in the organism which explains the higher AUC.

### 2.2. Route of administration

Oral formulations of moxidectin and ivermectin are available for sheep but not for goats. Nevertheless, they are widely used in goats at the same dose and several pharmacokinetic studies have been performed (Escudero et al., 1999; Gokbulut et al., 2007; Lespine et al., 2005; Scott et al.,