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Kinetics and anthelmintic efficacy of topical eprinomectin when given orally to goats

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ABSTRACT

Preliminary data suggest that topical eprinomectin in goat shows an individual variation in anthelmintic efficacy when used off-license at a dose rate of 0.5 or 1.0 mg/kg BW. As a result, the use of oral administration of topical formulation of eprinomectin tends to develop in dairy goat farms in France. The plasma levels and milk excretion as well as the anthelmintic efficacy of eprinomectin were determined in goats following oral administration of a topical formulation of the drug at dose rates of 0.5 and 1 mg/kg BW. The area under the concentration–time curve (AUC) values were 17.62 ± 9.68 ng day/ml and 6.56 ± 4.00 ng day/ml for plasma and milk respectively after the administration of 0.5 mg/kg BW and 45.32 ± 13.90 ng day/ml and 13.88 ± 1.77 ng day/ml for plasma and milk, respectively after the administration of 1 mg/kg BW. The milk-to-plasma ratio ranged from 0.33 to 0.36 and the amount of drug recovered in the milk was 0.4% of the total administered dose. The maximum concentrations of eprinomectin residues determined in milk after oral treatment were <20 μg/kg (Maximum Residue Limit in goat milk). The anthelmintic efficacy of the oral administration of topical eprinomectin was 100% through Faecal Egg Count Reduction Test in natural infection and ≥99.8% through Controlled Test in experimental infection (*Haemonchus contortus* and *Trichostrongylus colubriformis*). Additional information is needed about the fate of the vehicles used for topical formulation when given by oral route concerning food safety.

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1. Introduction

Eprinomectin [4″-(epiacetylamino)-4″deoxyavermectin B_1] is a member of the avermectin class of anthelmintic compounds, commercially launched in the late 90's as a novel avermectin. Besides broad-spectrum activity, it exhibits interesting low elimination in milk and was licensed, in lactating cows only, as a pour-on formulation with a zero milk withdrawal period. The high prevalence of resistance to benzimidazoles (BZD) in gastrointestinal nematodes in dairy goat in France ranges from 70 to 100% (Cabaret et al., 1995; Chartier et al., 1998, 2001) and severely compromises the nematode control. A few cases of levamisole resistance and a multiple anthelmintic resistance to BZD and levamisole case have also been described in dairy goat in France (Chartier et al., 2001; Paraud et al., 2009) and so far, no case of resistance against the avermectin-milbemycin group has been

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reported (Paraud et al., 2010). Therefore, the off license use ("cascade" regulation) of topical eprinomectin in France has progressively increased in dairy goat farms to tackle the ineffectiveness of BZD and it represents half of the drenching in some breeding areas today (Paraud, personal communication).

Previous data on efficacy and kinetics of topical eprinomectin in experimental conditions indicated that a higher dose rate had to be applied in goat compared to cattle, i.e. 1.0 instead of 0.5 mg/kg BW (Chartier et al., 1999; Chartier and Pors, 2004; Cringoli et al., 2004; Dupuy et al., 2001; Rehbein et al., 2014). Host physiology has also to be taken into account because of a reduced availability of eprinomectin in lactating compared to dry goats, probably related to a marked decrease in body fat reserves (Alvinerie et al., 1999; Dupuy et al., 2001; Lespine et al., 2012).

On the other hand, the licking behavior of ruminants can compromise efficacy because it leads to unexpected drug concentrations when macrocyclic lactones are administered topically (Bousquet-Mélou et al., 2011) although this habit seems more pronounced in cattle than in goat (Toutain et al., 2010). On the field, observations in goat have revealed ineffectiveness of topical eprinomectin on the basis of post-treatment faecal egg count (FEC) reductions (De Souza Chagas et al., 2007; Murri et al., 2014; Paraud et al., 2013). However, the delineation of a true resistance vs lower exposure/efficacy when facing "ineffectiveness" on the field is not possible and requires a preliminary definition of efficacious dose in case of off-license use and a laboratory controlled test with experimental infection (Paraud et al., 2013).

Given these circumstances, other routes of administration have been envisaged in order to ensure suitable and sustainable anthelmintic efficacy of eprinomectin in goats. It is well admitted that subcutaneous and oral routes of administration lead to higher drug concentrations in plasma and in tissues and to higher efficacy when compared with topical (Lespine et al., 2003, 2012). Results from Silvestre et al. (2007) and Chartier et al. (2013) showed that topical eprinomectin, when given per oral route (1 mg/kg BW), resulted in 100% efficacy (FEC) compared to 56–72% when given topically. In 2008, a French technical journal (*La Chèvre*, 2008, 284: 8) recommended to the farmers and veterinarians to use the topical eprinomectin in goat by oral route. However, the relationship between pharmacokinetic and efficacy has never been established for this formulation with this route of administration.

The first objective of this study was to determine the kinetics of eprinomectin in plasma and milk when topical formulation (Eprizero®, Bayer) is administrated *per os* in goat, at two dose rates of 0.5 and 1.0 mg/kg BW. The second objective was to assess the anthelmintic efficacy of such formulation and route of administration against natural or experimental infections with gastrointestinal nematodes using in vivo test (Faecal Egg Count Reduction Test and Controlled Test).

2. Material and methods

2.1. Pharmacokinetics study

Twelve lactating Saanen goats from a commercial cheese-producer flock of 120 were used. The animals grazed 8 months a year and were naturally infected with gastrointestinal nematodes. They were 2–7 year-old (2–7 lactations) and weighed 40–45 kg. Animals were randomly assigned to two groups of 6 animals: goats received 0.5 or 1 mg/kg bodyweight (BW) of topical eprinomectin (Eprizero®, Bayer) by oral route with a syringe.

Blood and milk samples were collected at milking parlour (2 milking operations per day) from each goat on 0, 0.5, 1, 1.5, 2, 5, 8, 12 days after drug administration and stored at −18 °C for 4 months until laboratory analysis.

The plasma and milk samples were analyzed for eprinomectin with high-performance liquid chromatography (HPLC) using a previously described method (Sutra et al., 1998). The quantification limit of the method was 0.07 ng/ml for both plasma and milk samples. The variation coefficients of the inter-assay precision analysis were 3.84 for plasma and 2.46 for milk.

The pharmacokinetic parameters were calculated using a non-compartmental analysis with version 4.2 of the Kinetica computer program (InnaPhase®, Philadelphia, PA). The area under the concentration–time curve (AUC) and the mean residence time (MRT) were calculated from $t = 0$ to the time of the last measurable concentration (t_{last}), using the arithmetic trapezoidal rule. The peak plasma concentration (C_{max}) and time of peak plasma concentration (T_{max}) were read from the plotted concentration versus time for each animal. Due to the small sample size, pharmacokinetic parameters between the dose rate groups were compared by a non-parametric Mann-Whitney test at a significance level of $p < 0.05$ (Statmost for Windows®, DataMost, Salt Lake City, 1994).

2.2. Anthelmintic efficacy study: natural infection and faecal egg count reduction test (FECRT)

Protocol and interpretation followed the guidelines of the World Association of Advancement of Veterinary Parasitology (WAAVP) (Coles et al., 1992).

Forty-five 2–7 year-old lactating housed Saanen goats from the same flock as above were weighed and then randomly assigned to 3 groups of 15 animals. Group 1 consisted in untreated animals while animals of the 2 other groups received 0.5 or 1 mg/kg BW of topical eprinomectin (Eprizero®, Bayer) by oral route with a syringe, respectively.

Faecal samples were rectally collected on day 0 and on day 16 post-treatment and stored 24 h at +4 °C before analysis. Individual faecal egg counts (Mc Master method) were performed according to Raynaud (1970) and expressed as eggs per gram of faeces (epg). The sensitivity of the McMaster technique was 50 epg.

The percentage reduction of Faecal Egg Count post-treatment was calculated as $FECR = (1 - T_{J16}/T_{J0} \times C_{J0}/C_{J16}) \times 100$ were C_{J0} and C_{J16} are the epg arithmetic

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