



# Getting the Best out of Ivermectin: Effect of Administration Route on Efficacy

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## **Summary**

The efficacy of different ivermectin formulations are comparably high although the oral drench seems to last shorter than the injectable and the pour-on formulations. Recognising the potential for the animal's physiological behaviour to assist drug action is of significant value.

Pour-on has become the route of choice in cattle thanks to its high efficacy and convenient application. However its marketing is hampered by the preference of many consumers being more directed towards other classical routes of administrations for no clear reasons. This should be tackled through intensified advertising campaigns and extension work.

The different coat nature of sheep, limits usage of pour-on formulations to cattle. The relatively short efficacy of orally administered ivermectin is the main disadvantage. This happens mainly when the drench bypasses the rumen while the rumen should work as a reservoir and a slow releaser.

Bypassing the rumen could be largely avoided with correct administration of the product. Using highly concentrated products (e.g. DUFAMEC DRENCH PLUS 1.02%), minimises the chance of the oesophageal groove closure taking place. Reducing the animal's feed intake 24 hours before drenching should significantly increase ivermectin's efficacy because large food intake increases gastric transit and consequently reduced the duration of drug availability. An oral paste formulation has widely replaced the injectable one in horse because it is effective and almost free of side effects. Combining ivermectin with an anti-tapeworm is highly recommended.

## **Introduction**

Ivermectin belongs to the macrocyclic-Lactones (ML) class of endectocides which, by increasing the membrane permeability to chloride ions, mediate the paralysis of the nematodes and certain classes of ectoparasites. Since the introduction of ivermectin in the beginning of the eighties, it became a revolution in the veterinary therapy thanks to its wide spectrum and high efficacy besides the fact that it is active at extremely low dosages.



The efficacy of antiparasitic drugs in general depends on toxic concentrations being presented to the parasite for sufficient time to lead to irreversible damage. The area under the plasma concentration curve (AUC) may reflect availability of the drug to the parasite and likely efficacy. Ivermectin persistence is a property of individual animal variation in addition to formulation, timing of treatment and parasite species (Yazwinski et al., 1994; Gayrard et al., 1999).

With the intention of making administration of ivermectin safer and less laborious in target species, different delivery methods are developed (injectable, pour-on and oral) and available formulations are being subjected to continuous improvement. However, this variation in administration routes should not be at the expense of having a good and constant bioavailability. We will try in this report to discuss those different formulations of ivermectin, possible differences in their efficacy and how to get the best possible results using them.

#### **Injectable formulations:**

It is established that subcutaneous injection is the most efficient route for ivermectin administration in terms of drug bioavailability in target animals when compared to oral and topical administration. Nevertheless, the fact that it is not practical for mass administration when there is a large number of animals to be treated and that it is only allowed to be administered by veterinarians, made availability of other formulations a great necessity. Furthermore, parenteral ivermectin is not used anymore in horses, at least officially, since it has been associated with additional side effects such as local reactions, swelling and pain and has widely been replaced by the oral paste formulation.

#### **Pour-on formulations:**

Pour-on formulation is recommended for mass use on cattle because of its ease of administration, absence of any visible side effects, high efficacy and also its long residual effects. It limits the risk of injury to user and animal and could be easily applied by farmers themselves. For these reasons, pour-on's have largely displaced therapeutically equivalent injectable formulations in farming practice and are routinely used to treat cattle. McKellar and Benchaoui (1996) reported that a transdermal formulation of ivermectin in cattle delivered at 500 µg/kg bodyweight is absorbed through the skin with an activity and persistence which were comparable to those of the injectable product against most parasites.



There were some worries earlier claiming that the efficacy of pour-on formulations are negatively affected by weather conditions (namely rain). However, results of different studies have proved that exposure of cattle to rain shortly before or after treatment has no impact on the efficacy of ivermectin pour-on therefore; precaution about treatment of wet animals or consideration of the potential for rain after treatment is not warranted (Rolfe et al, 1997; Rehbein et al., 1999).

However, the domain of the target animals of the pour-on is relatively limited. Wool and wool grease provide an almost impenetrable chemical and physical barrier which largely precludes this mode of administration from sheep, leaving it to be almost exclusively restricted to cattle (Hennessy et al., 1997). Furthermore, the concept of topical administration still has to fight against the market trend. The idea itself is just not accepted in some countries where farmers prefer to inject simply because they can not imagine that topical administration is capable of providing satisfactory systemic results. Continuous efforts exerted by veterinarians and extension workers are expected to overcome this kind of problems eventually.

#### **Oral formulations:**

Oral administration of ivermectin is popular mainly because farmers are able to carry it out themselves without having to wait for the vet and it is applicable mainly in sheep where topical administration is not relevant and in horses where it is the only available formulation now.

#### ORAL DRENCH FORMULATION:

This formulation has been shown to result in lower systemic availability of the parent compounds compared with the subcutaneous treatment (Marriner et al., 1987; Imperiale et al., 2004; Lespine et al., 2004). Nevertheless, some experimental data in sheep have shown that ML had a higher efficacy when given orally compared to subcutaneous route for both susceptible (Borgsteede, 1993) and resistant nematode strains (Gopal et al., 2001; Alka et al., 2004). In another study by Lespine et al. (2005) ivermectin provided similar efficacy against *T. colubriformis* after subcutaneous or oral administration in goats. However, on the basis of the lower ivermectin levels in tissues after oral administration it was suggested that the duration of efficacy may be shortened after oral compared to subcutaneous administration especially in animals with poor body condition in pasture where re-infection occurs quickly after anthelmintic treatment.

Normally rumen should work as a reservoir and a slow releaser. Ivermectin strongly associates with particulate matter in the rumen and the residence time of this complex provides the reservoir from



which absorption of drug from the rumen and from more distal site(s) following digesta passage is prolonged (Hennessy, 1997). The relatively short efficacy could be mainly attributed to the drench bypassing the rumen.

The act of drenching, particularly if the drench is presented to the buccal cavity, can stimulate closure of the oesophageal groove with significant drench bypassing the rumen in cattle (McEwan and Oakley, 1978) sheep (Prichard and Hennessy, 1981) and goats (Sangster et al., 1991). Absorbed drug concentrations may be initially higher, but are of such short duration that efficacy is reduced (Hennessy, 1997). This could be largely avoided with correct administration where the gun tip is placed over the tongue and the drench is dispensed directly into the oesophagus (Hennessy, 1997).

Large volume drench, administered to the buccal cavity also has the potential to bypass the rumen and result in much more variable between-animal drug availability than a small, more highly concentrated drench formulation (Scanda Techfile, Mallinckrodt Veterinary)(P.J. Martin, Personal communication) (Hennessy, 1997), possibly due to a higher incidence of oesophageal groove closure, reducing the amount of drench deposited in the rumen. Thus, products like DUFAMEC DRENCH PLUS 1.02%® (10.2 mg ivermectin per ml) which is almost 13 times more concentrated than standard products in the market, should guarantee a higher bioavailability for ivermectin.

Another thing, the duration of drug availability, once in the rumen, as it is absorbed and as it flows to more distal sites of absorption by host and parasite, largely depends on the flow rate of the digesta. Since rumen volume remains essentially constant, an inverse relationship between feed intake and digesta residence time exists (Kay, 1986) and a large food intake, particularly if the feed has a high water content, increases gastric transit and reduces the duration of drug availability. Several studies have conclusively demonstrated that the kinetic disposition of ivermectin on reduced feed intake is increased (Hennessy, 1997).

#### ORAL PASTE FORMULATION:

The paste formulation in horses has widely replaced the injectable one. It is proved to be a safe and effective antiparasitic for horses causing almost no detectable side effects at all. However, ivermectin is not effective against tapeworms which infect horses quite commonly. Even worse, using ivermectin alone might allow tapeworms to flourish after removing nematodes (Edwards, 1986; Owen et al., 1988; Coles et al., 2003). Therefore, a combination of ivermectin and praziquantel (an anti-tapeworm drug) in a paste formulation (DUFAMEC-P HORSEWORMER) should provide an excellent comprehensive approach to control parasitic infections in horses. The efficacy of ivermectin is not compromised by its combination with praziquantel and the two drugs do not overlap in their spectrum of activity (Barrett et al., 2004).



### **Conclusion:**

The efficacy of different formulations could be compared to each other although the availability of the oral drench is shorter than the rest. We can more effectively utilise the host's physiological responses to maximise drug availability. Efficacy of ivermectin is principally dependent upon the duration during which concentrations that are 'toxic' to the target parasites, are present (Lacey, 1988). The goal therefore must be to extend drug presence (obviously within safety limits) for as long as possible. Also any influence that can shorten the duration of drug availability and result in subtherapeutic or discriminating activity must be avoided since this action is a major contributor to the development of resistance. Ivermectin might be combined with other anthelmintics to broaden its spectrum when the occurrence of infections with worms which are not susceptible to ivermectin alone is highly expected.



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