

EFFICACY AND PERSISTENCE OF DORAMECTIN AND IVERMECTIN AGAINST NATURAL INFESTATIONS OF *DERMATOBIA HOMINIS* LARVAE IN CATTLE IN MINAS GERAIS.

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SUMMARY: A study was conducted in Florestal, Minas Gerais, Brazil, to evaluate the persistent efficacy of doramectin and ivermectin administered subcutaneously at a dose rate of 200 mcg/kg to cattle naturally infested by *Dermatobia hominis*. The persistence of doramectin was first evaluated in forty-six (46) crossbred Holstein by Zebu heifers, randomly allocated to 2 groups of 23 animals, based on the number of parasite nodules. Animals of T1 group received an injection of saline solution (1 mL/50 kg) and animals of T2 received an injection of doramectin (200 mcg/kg). *D. hominis* nodules were counted on days, -1, 15, 30, 37, 44, 51, 57, 64 and 72 post-treatment (p.t.). Doramectin was highly effective in removing *D. hominis* larvae during 37 days p.t.; new nodules began to appear only on day 44 p.t. but the efficacy of doramectin persisted higher than 90% until day 57. The difference between doramectin-treated and saline control was statistically significant ($p < 0.0001$). A second study comparing the persistence of doramectin and ivermectin against natural infestation of *D. hominis*, used sixty (60) castrated male crossbred Holstein-Zebu, randomly distributed to 3 groups of 20 animals based on the number of parasite nodules. Animals of T1 group received an injection of saline solution (1 mL/50 kg), animals of T2 received doramectin (200 mcg/kg) and animals of T3 received ivermectin (200 mcg/kg). *D. hominis* nodules were counted on days -1, 16, 30, 37, 44, 51, 58, 65, 72, 79, 86 and 93 p.t. Doramectin and ivermectin were highly effective in removing *D. hominis* larvae for 30 days p.t. From day 37 to day 72 p.t., animals treated with doramectin had significantly ($p < 0.05$) lower number of parasitic nodules than animals treated with ivermectin. The number of infested animals was significantly ($p < 0.05$) lower in doramectin-treated group than in the ivermectin group from day 37 to day 65. The efficacy of doramectin against *D. hominis* infestations persisted for 65 days higher than 90% compared to 44 days for ivermectin. The persistence of doramectin was at least 21 days longer than ivermectin.

KEY WORDS: Doramectin, ivermectin, tropical warble fly, persistent efficacy, *Dermatobia hominis*, cattle.

INTRODUCTION

Dermatobiosis is caused by the larvae of *Dermatobia hominis* fly, an obligatory parasite of domestics and wild animals, which affect also the humans. Its occurrence in bovines in Brazil, was reported by 76.4% of the 3,104 counties of Brazil participating in a nationwide epidemiological inquiry conducted by HORN & ARTECHE, (1985). Dermatobiosis do not occur in

the States of Amapá, Rondônia and Acre in the Northern region, and Ceará, Rio Grande do Norte and Sergipe in the Northeastern region, probably due to the climate conditions that are unsuitable for its survival. Annual economic losses of dermatobiosis in the South and Center American cattle are estimated to be in the order of 200 millions dollars (STEELMAN, 1976). With a complex biology, *Dermatobia hominis* utilizes other insects as vectors on which abdomen the gravid females

lay their eggs that are transported to the hosts. Once the vectors are in the hosts, the egg hatch originating small L1 larvae that penetrate actively the skin where they establish in subcutaneous nodules. The vast number of insects that serve as vector of *Dermatobia* (ARTIGAS & SERRA, 1965; RIBEIRO *et alii*, 1985), together with the diversity of hosts, contribute for their survival in the nature and making their control a difficult task. The control measures of dermatobiosis, are targeted to reduce its occurrence by improving the environmental hygiene to reduce the proliferation of the flies and mosquitoes, and/or the use of insecticides to reduce these insect vectors. Furthermore, to eliminate the larvae already infesting the hosts, there are used organophosphorous insecticides, closantel or ivermectins (GRAHAM *et alii*, 1958; ANDERSON, 1961; LOMBARDEO & FONTANA, 1968; MAGALHÃES *et alii*, 1980; CHAIA *et alii*, 1981; LOMBARDEO *et alii*, 1983; LEITE *et alii*, 1984; MAIA & GUIMARÃES, 1986). The efficacy and persistence of doramectin against *D. hominis*, was demonstrated by MOYABORJA *et alii*, (1993; 1997) in studies using induced infestation model in established cattle and the efficacy was confirmed by LEITE *et alii* (1996) under natural field infestation. OLIVEIRA *et alii* (1997) compared the persistence of doramectin and ivermectin in Rio Grande do Sul and demonstrated a persistence of at least 14 days longer for doramectin. The study reported here, was designed with the objective to confirm the duration of doramectin activity and to compare the persistent efficacy of doramectin and ivermectin against *Dermatobia hominis* infestations under natural field conditions in the State of Minas Gerais.

MATERIALS AND METHODS

The study was conducted in Florestal, MG, during the high incidence season of *D. hominis*. The persistence of doramectin against *D. hominis* infestations was first evaluated from October 1992 to January 1993 using forty-six (46) female crossbred Holstein by Zebu cattle naturally infested by *D. hominis*, selected from a bigger herd. The animals were selected based on their common origin and the number of nodules with live larvae of *D. hominis* counted on day -1. The presence of permanent humidity in the larvae fixation hole and the spontaneous movement of the larvae inside the nodule in response to light pressure with the fingers were used to determine the diagnostic of live larvae. On day -1, all experimental animals were identified with a white numbered ear tag, they were weighed and the number of nodules with live larvae of *D. hominis* were counted and recorded. Animals were then allocated randomly to two groups (T1 and T2) of 23 animals each, based on the number of nodules. For the allocation, the animals were ranked in descending order of the number of nodules and the first two animals of the list were assigned to groups T1 and T2. The procedure was repeated with the second pair of the list and thus successively until all 46 animals were allotted to T1 and T2. On day 0, animals of T1 group received an

injection of saline solution at a dose of 1 mL/50 kg of bodyweight and animals of T2 group received an injection of doramectin (Dectomax - Trade mark of Pfizer Inc., NY - USA) at a dose rate of 200 mcg/kg (1mL/50 kg). After treatment, all animals were returned to the original pasture temporarily divided in two equal paddocks where they were maintained separated throughout the study period. Nodules with live *D. hominis* larvae were counted in each animal on day -1 and on days 15, 30, 37, 44, 51, 57, 64 and 72 post-treatment (p.t.). On day 72, the study was terminated when the mean number of nodules in the doramectin-treated group returned to the initial level of infestation. In a second study, the persistence of doramectin and ivermectin was evaluated comparatively during March and June 1993. Sixty (60) crossbred Holstein-Zebu castrated male cattle, 10 to 38 months old, naturally infested by *D. hominis* were randomly distributed in 3 groups (T1, T2 and T3) of 20 animals each based on the number of parasitic nodules counted on day -1. The animals were ranked in descending order of the number of nodules present. The first 3 animals of the list were randomly allocated to the three treatment groups, T1, T2 and T3. The procedure was repeated with the second 3 animals of the list and thus successively until all 60 animals were allotted to the 3 groups. The animals were then individually weighed for calculation of treatment dose. On day 0, the animals were treated with a subcutaneous injection in the lateral midline of the neck. Animals of T1 group received an injection of saline solution (1 mL/50 kg), animals of T2 group were treated with doramectin (200 mcg/kg) and animals of T3 group were treated with ivermectin (200 mcg/kg). After treatment, all animals were returned to the original pasture where they were maintained together throughout the experimental period of 93 days. Observations were carried out on the day before treatment and on days 16, 30, 37, 44, 51, 58, 65, 72, 79, 86 and 93 p.t. when the number of nodules with live larvae of *D. hominis* were counted and recorded. The study was terminated for a treated group, when the number of nodules returned to initial level or when counts were stabilized for three consecutive counting. At the end of the study for a group, the animals were re-treated and released from the study.

Statistical analysis

The percent efficacy of doramectin or ivermectin treatment was calculated at each counting day, comparing the arithmetic mean number of parasitic nodules in the doramectin or ivermectin treated group to that of the control group, using the following formula:

$$\text{Efficacy (\%)} = \frac{\text{Arithmetic mean number of nodules in control group} - \text{Arithmetic mean number of nodules in treated group}}{\text{Arithmetic mean number of nodules in control group}} \times 100$$

In addition, natural logs (of nodule counts + 1) were analyzed with a one-way analysis of variance for each day on test when observations were made. The geometric mean of

nodule counts were calculated for each observation date and compared across the groups by analysis of variance (Proc. GLM, SAS Institute Inc., Cary, N.C.). The level of rejection of null hypothesis was set at $\alpha = 0.05$.

RESULTS AND DISCUSSION

In the study 1, doramectin was 100% efficacious in eliminating the parasite nodules until day 37 p.t. (Table 1). The efficacy of doramectin persisted higher than 90% until day 57 p.t. Compared with the control group, the number of nodules counted in the doramectin-treated group was significantly lower ($p < 0.0001$) at each observation day until the end of the study on day 72. In the control group treated with saline solution, the number of nodules continued to increase progressively achieving a peak on day 51 with a mean of 107 nodules per animal, which demonstrated the high challenge infestation that the animals were exposed. Furthermore, when compared the number of animals free of infestation, the doramectin-treated group had a significantly higher ($p < 0.05$) number of animals without *D. hominis* nodules than saline-treated control (Table 2). These results reinforce the concept of prolonged bioavailability of the product evidenced by WICKS *et alii* (1993), confirm the efficacy of doramectin against induced (MOYA-BORJA *et alii*, 1993) and natural (LEITE *et alii*, 1996) *D. hominis* infestation, and also confirm the persistence of doramectin beyond the 35 days reported by MOYA-BORJA *et alii* (1993; 1997). In study 2, doramectin and ivermectin were highly efficacious in removing *D. hominis* nodules (Table 3). From an initial mean of 33 parasitic nodules per animal in the ivermectin-treated group, no nodules were observed on day 30 p.t., and in the doramectin-treated cattle, only one animal continued with 2 nodules on day 30. From day 37 to day 72 p.t., the animals treated with doramectin had a mean number of nodules significantly lower ($p < 0.05$) than in the group treated with ivermectin and the number of infested

animals was also significantly lower ($p < 0.05$) in the doramectin-treated group from day 37 to day 65 p.t. (Figure 1). On day 72 p.t., the experiment was terminated for the ivermectin group when the number of nodules returned to the initial counts. The doramectin group was terminated on day 93 p.t. without returning to initial level. The period of protection with efficacy higher than 90% was 44 days for ivermectin and 65 days for doramectin indicating a difference of 21 days longer for doramectin. The results reported here with doramectin, are in agreement with the results obtained by others in terms of efficacy and also in terms of duration of protection that was more than 35 days against induced (MOYA-BORJA *et alii*, 1993; 1997) or natural (OLIVEIRA *et alii*, 1997) infestations. On the other side, the results with ivermectin are also in agreement with other studies which demonstrated high efficacy (LEITE *et alii*, 1984; MAIA & GUIMARÃES, 1986; RONCALLI & BENITEZ-USHER, 1982) and complete persistence for 4 weeks (BORJA *et alii*, 1997). In a similar study in Rio Grande do Sul State, OLIVEIRA *et alii* (1997), observed complete efficacy at day 31 with ivermectin and day 45 with doramectin. Ivermectin had already some animals with reinfestations on day 38, while in the doramectin-treated group, reinfestations started to appear only on day 52 p.t., resulting in a 14 days advantage for doramectin. Notwithstanding the difference of the period of protection determined in the various studies mentioned, due to variations in the regional epidemiological conditions, it can be considered that the results are very similar in the studies conducted for efficacy and also for persistence. This fact, can be related to the great efficiency and stability of the molecules tested, keeping in mind the differences in potency between doramectin and ivermectin against *D. hominis*. Reinforcing this hypothesis the animals were in the same pasture subjected to same level of challenge and as observed in the animals of the control group, the pressure of infestation was very high during all the experimental period showing the high level of challenge that the products were exposed. Under these conditions, it was

Table 1 - Mean number of *Dermatobia hominis* nodules and percent efficacy of doramectin at each observation day (Study 1).

Days on Test	Saline Solution		Doramectin Treatment		Percent Efficacy VS Control
	Number of Animals	Mean Nodules/ Animal	Number of Animals	Mean Nodules/ Animal	
-1	23	26.52a	23	24.74a	-
15	23	29.87a	23	0b	100.0
30	23	62.87a	23	0b	100.0
37	23	91.35a	23	0b	100.0
44	23	96.83a	23	1.17b	98.79
51	23	107.65a	23	2.00b	98.14
57	23	89.48a	23	6.39b	92.86
64	23	94.30a	23	13.43b	85.76
72	22*	66.05a	23	22.04b	66.63

a, b = Between treatments, means with different letters are significantly different ($p < 0.0001$).

* One animal of group T1 was not found on day 72.

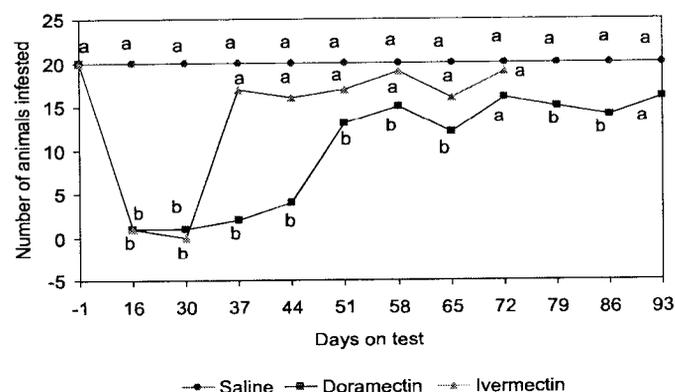
possible to differentiate the products in terms of duration of persistence, confirming the results obtained by OLIVEIRA *et alii*, (1997), in Rio Grande do Sul. Furthermore, it can be seen in Figure 1, the evolution of the number of infested animals

according to the treatment. While the control group had all the 20 animals infested during the whole experimental period, the animals in T3 group treated with ivermectin, had zero infestation on days 16 and 30 p.t. but, from day 37 onward, the number of infested animals was statistically similar ($p > 0.05$) to the control group. In group T2 doramectin-treated, the level of infestation dropped near to zero and remained significantly lower ($p < 0.05$) than that of ivermectin until day 65 p.t. The results obtained in this study, confirm the persistence of at least 21 days longer for doramectin in the control of *D. hominis* infestations compared to ivermectin.

Table 2 - Number and percentage of animals free of *Dermatobia hominis* nodules at each observation day following treatment with doramectin or saline solution (Study 1).

Days on Test	Saline Solution N = 23		Doramectin Treatment N = 23	
	Number of Animals Free of Nodules	Percent	Number of Animals Free of Nodules	Percent
-1	0	0	0	-
15	0	0	23	100.0
30	0	0	23	100.0
37	0	0	23	100.0
44	0	0	18	78.3
51	0	0	18	78.3
57	0	0	9	39.1
64	0	0	4	17.4
72	0	0	0	0.0

Figure 1 - Number of animals with *Dermatobia hominis* nodules at each observation day (Study 2).



a, b = Between treatments, means with different letters are significantly different ($p < 0.0001$).

* One animal of group T1 was not found on day 72.

a, b = Between treatments, different letters are significantly different ($p < 0.05$).

Table 3 - Arithmetic mean number of *Dermatobia hominis* nodules in cattle treated with doramectin or ivermectin and percent efficacy (Study 2).

Days on Test	Saline Solution		Doramectin Treatment		Ivermectin Treatment
	Mean Number Nodules/Animal	Mean Number Nodules/Animal	Percent Efficacy	Mean Number Nodules/Animal	Percent Efficacy
-1	31.65a	30.35a	0	32.65a	0
16	32.80a	0.15b	99.54	0.05b	99.85
30	50.65a	0.10b	99.80	0.00b	100
37	77.40a	0.70c	99.10	3.65b	95.28
44	71.70a	1.20c	98.33	4.85b	93.24
51	91.25a	3.35c	96.33	10.70b	88.27
58	83.20a	5.10c	93.87	16.10b	80.65
65	94.95a	7.50c	92.10	25.55b	73.09
72	97.00a	11.95c	87.68	45.40b	53.20
79	99.80a	16.45b	83.52	*	-
86	85.45a	20.00b	76.59	*	-
93	86.60a	23.85b	72.46	*	-

* Study was terminated for the group when infestations returned to initial level.

a,b,c = Between treatments, means with different superscripts are significantly different ($p < 0.05$).

SUMÁRIO

Um estudo foi conduzido em Florestal, Minas Gerais, Brasil, para avaliar a eficácia persistente de doramectin e ivermectin administrados via subcutânea na dose de 200 mcg/kg em bovinos naturalmente infestados por larvas de *Dermatobia hominis*. A persistência de doramectin foi primeiro avaliada em 46 novilhas mestiças Holandes-Zebu, distribuídas em dois grupos de 23 animais cada, baseado no número de nódulos parasitários. Os animais do grupo T1 receberam uma injeção SC de solução salina (1 mL/50 kg) e os animais do grupo T2 receberam doramectin (200 mcg/kg). Nódulos de *D. hominis* foram contados nos dias -1, 15, 30, 37, 44, 51, 57, 64 e 73 pós-tratamento (p.t.). Doramectin foi altamente efetivo na remoção das larvas de *D. hominis* durante 37 dias p.t.; novos nódulos começaram a aparecer somente no dia 44 p.t., mas a eficácia de doramectin persistiu acima de 90% até o dia 57 p.t. A diferença entre doramectin e solução salina foi estatisticamente significativa ($p < 0,0001$). Um segundo estudo comparando a persistência de doramectin e ivermectin contra infestação natural de *D. hominis* foi realizado em 60 bovinos machos castrados mestiços Holandes-Zebu, distribuídos em 3 grupos de 20 animais cada baseado no número de nódulos parasitários. Os animais do grupo T1 receberam injeção de solução salina (1 mL/50 kg), os animais do grupo T2 receberam doramectin (200 mcg/kg) e os do grupo T3 receberam ivermectin (200 mcg/kg). Contagens de nódulos parasíticos foram realizadas nos dias -1, 16, 30, 37, 44, 51, 58, 65, 72, 79, 86 e 93 p.t. Doramectin e ivermectin foram altamente efetivos na remoção de larvas de *D. hominis* por 30 dias. A partir do dia 37 até o dia 72, os animais tratados com doramectin tiveram número de nódulos significativamente ($p < 0,05$) menores do que os animais tratados com ivermectin. O número de animais infestados foi significativamente ($p < 0,05$) menor no grupo tratado com doramectin do dia 37 ao dia 65 p.t. A eficácia de doramectin contra as infestações por larvas de *D. hominis* persistiu por 65 dias acima de 90% comparado com 44 dias para ivermectin. A persistência de doramectin foi pelo menos 21 dias mais prolongada do que a do ivermectin.

PALAVRAS-CHAVE: Doramectin, ivermectin, berne, eficácia persistente, *Dermatobia hominis*, bovinos.

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