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Therapeutic and Persistent Efficacy of Doramectin Against Nematode in Swine Infected Naturally in China

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Abstract: The purpose of this study was to evaluate the treatment efficacy of 1% doramectin injection against nematode in swine infected naturally in China and determine dosage regimen of doramectin in swine. A controlled clinical study was conducted on 200 swine infected with nematode naturally in Lanzhou. The tested groups included doramectin 400, 300 and 150 μg kg^{-1} by IM, ivermectin 300 μg kg^{-1} by SC as drug control group and blank control group. The results showed the efficacy against nematode of high dosage doramectin (400 μg kg^{-1}) was significantly difference from middle and low dosage group ($p<0.05$) and was significantly difference from control ivermectin group ($p<0.01$). The persistent period of nematocidal with high, middle and low dosage were 28, 28 and 21 days, respectively. The body weight gain of high, middle dosage doramectin and ivermectin group were significantly difference from the low dosage doramectin and untreated control ($p<0.05$ and $p<0.01$). So, the recommended dosage regimen of doramectin against swine's nematode was 300 μg kg^{-1} body weights by IM for once administration of medicine.

Key words: Doramectin, nematode, swine, therapeutic efficacy, China

INTRODUCTION

Avermectins which are the product fermented from *Streptomyces hydroscopious* or *Streptomyces avermitilis* belong to edaphon have highly efficacious vermicide to kill nematode and ectozoa (Firkins *et al*., 2001; Mehlhorn *et al*., 1993). Presently, avermectins have become the most important anti-parasitic agent and have been broadly used in livestock's parasite therapeutic and protective purpose. Doramectin is a broad-spectrum and current parasiticide in animal which is one of the avermectin derivatives and fermented from a bioengineering bacterium (Goudie *et al*., 1993). The mechanism of doramectin killing parasite is as same as ivermectin which resists parasite by intensifing the activity of γ-Aminobutyric Acid (GABA) (Blackhall *et al*., 2003). Most of the recent evidences suggest that the avermectin/milbemycin family of anthelmintics act via specific interactions with glutamate-gated chloride channels (Yates *et al*., 2003).

Nematode parasitized in swine will affect swine breeding capability, retard swine's growth and weight gain, waste feed, further more it will easily bring on the secondary affections, so, it has been considered to be harm for swine industry. In order to develop swine industry, it is very significant to prevent and cure parasite in swine. It has been reported that doramectin has highly efficacious for treatment nematode in cattle (Ballweber *et al*., 2000; Loyacano *et al*., 2001), swine (Firkins *et al*., 2001; Reina *et al*., 2000; Stewart *et al*., 1996), sheep (Dorchies *et al*., 2001; Hertzberg *et al*., 2001), horse (Cirak *et al*., 2007; Davies and Schwalbach, 2000) and other animals (Molina *et al*., 2005; Murayama *et al*., 2010) and doramectin medicaments used in veterinary clinical in China have been only imported yet with high price. Recently, the studies of doramectin stuff and pharmaceutics have been accomplished in China (Zhang *et al*., 2005).

This study was carried out to confirm the efficacy of 1% doramectin injection in swine and ascertain its dosage regimen to be used.

MATERIALS AND METHODS

Reagents: About 1% doramectin injection which was testing pharmaceutical was made by Lanzhou Institute of

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Husbandry and Pharmaceutical Sciences of CAAS and Zhejiang Hisun Pharmacy Co., Ltd. and batch number was 20030102.

About 1% ivermectin injection which was control pharmaceutical was purchased from Shanghai Tongren Pharmaceutics Company and batch number was 100512.

Animal and groups: About 200 swine which infected with gastrointestinal nematodes and lung-worm naturally were selected by collecting the recta feces and checking the Eggs Per Gram (EPG) with saturated saline flotation method (McMaster's Method) (Wang, 2003). All swine coming from farmer around Lanzhou were the f2 swine (Yorkshire x Landrace) and the local crossbred swine and weighing 14~21 kg and approximately 50~70 days old. The results of feces eggs checking were positive and all these swine had been badly infected with the nematode. These swine were divided into 10 groups at random according weight, EPG and parasite.

This study included 2 experiments. The first experiment was carried out for testing efficacy of the doramectin injection on treating nematode, three doramectin groups composed of 3 different dosage (high, middle and low dosage separately) and one ivermectin group and normal saline control group, the dosage and animals are showed in Table 1. And the second experiment was performed to assess the drug duration of action which composed of three doramectin groups and also designed one ivermectin group and one control group; the dosage and animals are showed as in Table 2.

Table 1: The dosage and pigs of efficacy study

	Doramectin				
Groups	High	Middle	Low	Ivermactin	Control
Pigs	20	40	20	20	20
Dosage ($\mu g\ kg^{-1}$ BW)	400 (IM)	300 (IM)	150 (IM)	300 (SC)	0

Table 2: The dosage and pigs of study for action duration

	Doramectin				
Groups	High	Middle	Low	Ivermactin	Control
Pigs	10	40	10	10	10
Dosage ($\mu g\ kg^{-1}$ BW)	400 (IM)	300 (IM)	150 (IM)	300 (SC)	0

Methods: Fecal eggs checking per gram were performed by McMaster's Method (Wang, 2003). Eggs of trematode and cestode were not counted as avermectins do not have efficacy for them.

Nematode checking in swine: Anatomize the swine and separately sampling lung, stomach, small intestine and large intestine, wash and precipitate and then anatomize. These animal studies adhered to the ethical requirements of China.

Statistical analysis: In the first experiment, the percentage of doramectin efficacy against nematode was assessed according to Rough Anthelmintic Rate (RAR), Accurate Anthelmintic Rate (AAR), Deworming Clean Rate (DwCR) and Nematodes Eggs Reduction Rate (NERR) and calculated according to the following formulae (Wang, 2003).

Rough Anthelmintic Rate (RAR):

$$RAR = \frac{\text{Mean of residue nematodes of blank controlgroup} - \text{Mean of residue nematodes of test group}}{\text{Mean of residue nematodes of blank control group}} \times 100\%$$

Accurate Anthelmintic Rate (AAR):

$$AAR = \frac{\text{Expelled nematodes}}{\text{Expelled nematodes} + \text{Residue nematodes in body}} \times 100\%$$

Deworming Clean Rate (DwCR):

$$DwCR = \frac{\text{Test animals} - \text{Nematode postive animals}}{\text{Test animals}} \times 100\%$$

Nematodes Eggs Reduction Rate (NERR):

$$NERR = \frac{\text{EPG of pretreatment} - \text{EPG of posttreatment}}{\text{EPG of pretreatment}} \times 100\%$$

Clinical observation and body weight gain: The swine's spirit, appetite, expelling worms and adverse reaction to treatment were observed. The date of swine's weight gain was dealt with statistical analysis at the end of the experiment. Rates of live weight gain of each treatment group were calculated by the following formulae:

$$\text{Rate of live weight gain} = \frac{\text{Mean of test group's live weight gain}}{\text{Mean of blank control group's live weight gain}} \times 100\%$$

RESULTS

Swine nematode epidemic (infections) investigation: The faecal egg examination before and after treatment indicated that the swine had been mix-infected with a great variety of nematode. According the number of parasite, they were *Oesophagostomum dentatum*, *Globocephalus longemucronatus*, *Trichuris suis*, *Strongyloides ransomi*, *Bourgelatia diducta* and *Metastrongylus pudendotectus* in turn. The rates of faecal egg examination are listed in Table 3.

Therapeutic efficacy: Results of the first experiment (Table 4) showed that the AAR of high, middle and low dosage doramectin group and the control ivermectin group were 100, 98.67, 98.09 and 97.22%, respectively. The RAR were 100, 98.75, 98.75 and 97.50%, respectively, there was no significantly difference ($p>0.05$) between those groups. The DwCR were 100, 90, 80 and 75%, respectively. The result indicated the high dosage doramectin group has significantly difference from middle and low dosage group ($p<0.05$) and also has distinct significantly difference from control ivermectin group ($p<0.01$).

The necropsy results were identical to the faecal egg count results in principle. The most nematodes were *Oe. dentatum* and *G. longemucronatus*, the following were *B. diducta* and *T. suis*. The least nematoden was *S. ransomi*. The nematode had been chiefly parasitizing in segmented intestine and blind gut. A few nematodes had been detected in stomach and small intestine. The lungworms had not been detected.

Investigation of the persistent nematocidal time of doramectin in swine *in vivo*: The statistical results of the persistent nematocidal time of doramectin in swine *in vivo* had been shown in Table 5. The persistent nematocidal time had been calculated through the results of faecal egg count in the second experiment. Fecal samples were collected from each animal immediately before treatment and on days 7, 14, 21 and 28 following treatment during the experiment. The 100% NERR of high dosage doramectin had taken place on the 0~28 days after treatment. The middle dosage were on the days 7~28. The low dosage were on the days 7~21. The 100% NERR of the ivermectin group were on 7~14 days. According to this result, a conclusion were made that the persistent of the high, middle and low dosage doramectin and the

Table 3: Swine nematode epidemic investigation

Species	Positive pigs	Positive rate (%)	Mean of EPG	Infection rate (%)*
Oe. dentatum eggs	189	94.5	71.40	44.40
G. longemucronatus eggs	108	54.0	43.89	27.29
T. suis eggs	107	53.5	35.34	21.98
S. ransomi eggs	45	22.5	6.50	4.04
B. diducta eggs	26	13.0	2.30	1.43
M. pudendotectus eggs	13	6.5	1.37	0.85

*Infection rate = (Mean of EPG/Mean of per pig's EPG)×100%, Mean EPG of each pig = 160.80. The total number of pigs was 200

Table 4: The statistical results of therapeutic efficacy

		Necropsied						
Drugs	Dosage (μg kg^{-1})	Pigs	Expelled nematodes	Pigs	Positive	Residue nematodes	RAR (%)	AAR (%)	DwCR (%)
Doramectin	400	20	295	20	0	0	100.00	100.00	100
Doramectin	300	40	595	40	4	8	98.75	98.67	90
Doramectin	150	20	205	20	4	4	98.75	98.09	80
Ivermectin	300	20	280	20	5	8	97.50	97.22	75
Control	0	20	15	20	20	320	0.00	4.48	0

Table 5: The investigation on persistent nematocidal time of doramectin in swine *in vivo*

			Post-treatment (days)													
Drug and dosage		EPG	Positive pigs and EPG					NERR (%)					DwCR (%)			
(μg kg^{-1})	Pigs	0 day	7	14	21	28	35	7	14	21	28	35	7	14	21	28	35
Doramectin 400	10	249.8	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	100.00	100	100.00	100.00	99.96	100	100	100	100	90
Doramectin 300	40	206.4	4 (0.35)	0 (0)	0 (0)	0 (0)	2 (0.2)	99.83	100	100.00	100.00	99.90	90	100	100	100	95
Doramectin 150	10	255.3	3 (0.1)	0 (0)	0 (0)	1 (0.1)	4 (0.8)	99.96	100	100.00	99.96	99.69	70	100	100	90	60
Ivermectin 300	10	225.7	3 (0.1)	0 (0)	2 (0.3)	3 (0.9)	4 (2.3)	99.96	100	99.87	99.60	98.98	70	100	80	70	60
Control	10	225.8	10 (225.9)	10 (225.8)	10 (225.8)	10 (225.8)	10 (243.9)	0.00	0	0.00	0.00	0.00	0	0	0	0	0

Table 6: Live weight gain

Groups and dosage (μg kg^{-1} BW)	Pigs	Mean of body weight (kg) Pre-treatment	28 days post-treatment	Rate of live weight gain (%)
Doramectin 400	10	18.90±1.93	23.56±2.11	158.59^{a}
Doramectin 300	40	18.15±1.57	22.67±1.74	153.74^{a}
Doramectin 150	10	18.43±2.06	21.95±2.22	120.75^{b}
Ivermectin 300	10	17.79±2.21	22.39±1.98	159.52^{a}
Control group	10	18.35±1.62	21.29±2.36	100.00^{b}

The same letter shows no significant difference ($p>0.05$) and the different letters show significant difference ($p<0.05$)

control ivermectin groups were respective 28, 28, 21 and 14 day. Therefore, the middle dosage doramectin was selected for the clinical usage.

Clinical observation and live weight gain: Clinical signs and live weight gain had been observed in the study. None of the swine in treatment groups showed the clinical symptoms of parasitic infection and any adverse reactions following the administration of doramectin and ivermectin. On the contrary, the control group swine behaved gnawing, scratching, groveling and rubbing in wall, etc. These swine of control group showed emaciated body although consumed lots of food.

Results of live weight gain obtained during the second study are shown in Table 6. The groups which treated with doramectin and ivemectin, had greater weight gain rate from days 0-28 than the control group (158.59, 153.74, 120.75 and 159.52% in the high, middle, low dosage doramectin and ivermectin treatment group versus 100.00% in the control group). There were no significant statistically difference of the high dosage doramectin and ivermectin from the middle dosage doramectin group and the difference of low dosage doramectin from control group was not significant too ($p>0.05$). However, there were significant statistical differences of high, middle dosage doramectin and ivermectin from low dosage doramectin or control ($p<0.05$ and $p<0.01$).

There was no clinical pathological abnormity but the pig's ache reactions were observed when they had been administrated doramectin and ivermectin for a few minutes.

DISCUSSION

The results of faecal egg examination indicated that all experimental swine had been infected with *Oe. dentatum*, *G. longemucronatus*, *T. suis*, *S. ransomi*, *B. diducta*, *M. pudendotectus*, etc. *Oe. dentatum* egg developed into imago after 38 days infected with piglet. *T. suis* egg did after 30~40 days infected with piglet. *G. longemucronatus* did after 25~60 days infected with piglet. All these three kinds of eggs had been checked in the piglets. The infected ratio and intensity of the three nematodes were higher than others. These indicated that the swine had been intensively infected by the nematode and each pig was usually infected with 4~5 sorts of nematodes.

The therapeutic efficacy of high, middle and low dosage doramectin groups and control ivermectin group were credibility for expelling nematodes in swine. But the high and middle dosage doramectin groups were more efficacious than the low dosage group and ivermectin group. The time of persistent nematocidal activity of doramectin was 28 days. According to the results, the recommended dosage regimen of doramectin in swine was 300 μg kg^{-1} body weights by intramuscular injection for once administration of medicine.

CONCLUSION

At present, ivermectin has been often used to treat parasite in veterinary clinical in China by injecting twice a week interval into animal (Cai *et al*., 2006; Ji *et al*., 2010; Liu *et al*., 2011). According to those studies, the time of persistent nematocidal activity of ivermectin were 7 days, therefore, it is necessarily to treat with ivermectin twice a week interval. Although, doramectin as a current treating parasite medicine is more expensive than ivermectin, the market prospect of doramectin is still very bright because of its long effect and convenience in clinic.

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