THE ANTICOCCIDIAL ACTIVITY OF SACOX IN FATTENING RABBITS

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Abstract - In three separate infection trials using an inoculum of 5 x 10 Eimeria magna (trial 1), 5 x 10 Eimeria intestinalis (trial 2) or 4 x 10 Eimeria stiedai (trial 3) per animal, the dose response of 7.5, 15.0, 22.5 and 30.0 ppm Salinomycin sodium (Sacox, Hoechst AG) was tested in male New Zealand White. An uninfected, unmedicated and an infected, unmedicated group served as controls. During the critical period of E. magna and E, intestinalis infections, 15.0, 22. 5 and 30.0 ppm Sacox had a significant favourable effect on feed intake and weight gain compared to the infected, unmedicated control. Total oocyst output was reduced by 84.3, 92.9 and 88.6 % in trial 1 and 82.9, 89.6 and 94.3 % in trial 2. E. stiedai species responded best to 22. 5 ppm and 30.0 ppm Sacox. Both dosages avoided significantly the decrease of feed intake and weight gain depression during the critical phase of infection. The relative liver weight (% of body mass) of 5.8 % in the infected control was significantly reduced to 3.7 % and 3.2 %, the lesion score was reduced from 3.2 to 0.7 and 0.3 respectively.

INTRODUCTION

Coccidiosis in rabbits is still a major threat in intensive rearing causing significant weight gain depression, bad feed conversion or even high mortality. Besides consequent hygienic management, the prophylactic use of anticoccidials in feed is necessary to avoid any risk of an outbreak of coccidiosis.
Sacox (Salinomycin sodium, Hoechst AG) is one of the world's leading anticoccidials in broiler production. In addition, many authors have described a good efficacy against Eimeria species of the rabbit in laboratory and field trials. [LÄMMLER and HEIN (1980), OKERMAN and MOERMANS (1980), SAMBETH and RAETHER (1980), KUTZER *et al.* (1981), PEETERS *et al.* (1982) GALLAZI *et al.* (1983), COUDERT (1989)].
However the dosages tested varied in a large range. The present study was initiated to examine the dose dependant response of relevant Eimeria species of the rabbit to Sacox in three separate infection trials.

MATERIALS AND METHODS

Three separate infection trials were conducted in Hoechst owned research facilities corresponding to the principles of GLP (good laboratory practice). On day of arrival, the rabbits were vaccinated against hemorrhagic virus disease. In each trial, 42 coccidia free male New Zealand White, 9 weeks old, were - after an adaptation period of 2 weeks - randomised into six groups with seven rabbits each: A: uninfected, unmedicated control (UC), B: infected, unmedicated control (IC), C - F: infected, 7.5, 15.0, 22.5, 30.0 mg Sacox/kg feed. Pelleted all-mash feed with 17.2 % crude protein and 11.6 % crude fibre and water were supplied *ad libitum*. Application of medicated feed started one day prior to infection. The correct concentrations of Sacox in the feeds were confirmed by the Turbidimetric assay (Quality Control Feed Additives, HVG). The rabbits were kept individually in cages of 1,705 cm². On the second day of the trials (DO), the animals were inoculated with either E. magna (trial 1), E. intestinalis (trial 2) or E. stiedai (trial 3). Table 1 gives information on the infections and the respective trial duration.

Table 1 : Description of the infection and trial duration

Trial No.	Eimeria species[1]	Inoculation dose/animal (no. of sporulated oocysts)	Trial duration*
1	E. magna	5×10^4	D - 1 till D + 15
2	E. intestinalis	5×10^3	D - 1 till D + 16
3	E. stiedai	4×10^4	D - 1 till D + 34

* D0 = day of infection ; [1] Origin of strains : P. COUDERT, INRA, Station de Pathologie Aviaire et de Parasitologie, F - 37380 Monnaie, France.

Daily feed intake and weight gain were measured individually. After termination of the prepatent period, starting D +5 in the E. magna groups, D +7 in the E. intestinalis groups and D +14 in the E. stiedai groups, daily oocyst output was counted per animal (modified method after WETZEL, 1951). Additionally, relative liver weight and liver lesions were determined after slaughter of the animals in trial 3. The results are reported considering three different phases of the trial : the prephase comprises the period from trial start to appearance

of first symptoms. The critical phase includes the pathological state followed by the recovery phase lasting to termination of the trials. According to the different endogenous development cycles of the Eimeria species used for infection, the three phases vary for each trial (see Tables 2 - 4). For statistical analysis, the paired t-test (one-sided) was used (HOTHORN and LEHMACHER, 1991) to evaluate differences in feed intake and weight gain and the pairwise Wilcoxontest, one-sided (HOLLANDER and WOLFE, 1973) for the parameters oocyst excretion, liver weight and lesion score. The uniform level of significance was 5 %.

RESULTS AND DISCUSSION

Under the conditions of these trials, no coccidiosis related mortality occurred. However, the chosen inoculation doses of 5 x 10 sporulated oocysts of E. magna (trial 1) and 5 x 10 of E. intestinalis (trial 2) caused significant intestinal coccidiosis and diarrhoea in the infected controls accompanied by a temporary impact of the general condition. 4 x 10 sporulated oocysts of E. stiedai (trial 3) led to a distinct disruption of the liver function due to obstruction of the bile ducts and damage of the parenchyma in the infected control.

Trial 1 : Infection with E. magna (Table 2)

In the prephase of this trial, the 30.0 ppm Sacox group showed a significant lower feed intake (- 30.6 %) than the uninfected control having no significant influence on the weight gain development. During the critical phase, running parallel to the development of schizonts and gamonts in the small intestine, a lower, not significant feed intake in the infected control was observed. In the same phase, the weight gain development of all medicated groups was significantly better than in the uninfected control. The weight gain during the recovery phase, after the maximum excretion of oocysts, exhibited no significant differences, though the animals of the infected control overcompensated weight gain during some days of this period. The prepatent period of E. magna is described in the literature with 7 (COUDERT *et al.*, 1989) or 7 - 9 days (ROMMEL, 1992). The strain used for artificial infection in this trial led in some cases (i.e. group D) already to an earlier excretion. Group B (IC) and C (7.5 ppm Sacox) showed marked diarrhoea due to coccidiosis during the prepatent and patent period including a temporary depression of the general behaviour. Accordingly, the oocyst excretion was only moderately lowered (- 26,1 %). The groups with 15.0, 22.5 and 30.0 ppm Sacox reduced significantly oocyst excretion by 84.3, 92.9 and 88.6 % respectively.

Table 2 : Overview of daily feed intake and weight gain as well as total oocyst output during infection with E. magna (trial 1)

Trial group	A	B	C	D	E	F
Feed intake g/d						
D-1 till D+3	122.1[a]	122.7	117.7	114.0	100.3	84.8[b]
	21.1	*22.8*	*20.3*	*32.5*	*16.2*	*31.6*
D+4 till D+7	110.0	64.1	98.2	99.6	98.9	88.8
	35.2	*6.6*	*20.9*	*41.2*	*22.4*	*35.9*
D+8 till D+15	102.9	103.7	103.7	115.0	90.1	95.2
	43.3	*11.4*	*24.0*	*24.3*	*19.5*	*23.3*
Weight gain g/d						
D-1 till D+3	17.9	27.3	20.8	19.5	10.7	12.5
	27.8	*30.7*	*24.0*	*24.6*	*25.3*	*29.7*
D+4 till D+7	12.8	-28.0[a]	2.9[b]	12.3[b]	14.3[b]	10.2[b]
	27.8	*16.4*	*8.9*	*16.4*	*9.0*	*13.7*
D+8 till D+15	13.2	28.3	17.0	22.3	14.3	17.4
	26.1	*4.8*	*7.9*	*6.0*	*5.3*	*4.7*
Total oocyst output	0.0	96 787.6[a]	71 556.0	15 204.3[b]	6 909.3[b]	11 000.7[b]
(D+5 till D+15)		*14 718.4*	*29 117.6*	*23 301.7*	*6 829.3*	*12 634.9*
Reduction to B (%)		0.0	26.1	84.9	92.9	88.6

[ab] different superscripts are significantly different ($p<0.05$) ; Values in italic letters refer to standard deviation of the mean.

Trial 2: Infection with E. intestinalis (Table 3)

During the prepatent and patent period, the animals of group B (IC) and C (7.5 ppm Sacox) reacted with distinct diarrhoea due to coccidiosis and significant weight depression. The general behaviour was moderately influenced. The infection caused by this very pathogenic Eimeria species resulted in a significantly increased average feed intake in the groups E and F (22.5 and 30,0 ppm Sacox) during the critical phase compared to the

infected control. No further difference in feed intake was noted in any other phase. The daily weight gain during the critical phase was superior for the 15.0, 22.5 and 30,0 ppm Sacox medicated groups. Group C (7.5 ppm) prevented daily weight depression only moderately. Apparently, the weight gain development in the infected control was still retarded in the recovery period - however due to high individual deviations this difference was not statistically significant. The oocyst output was significantly reduced in all medicated groups, with increasing dosages of 7.5, 15.0, 22.5 and 30. 0 ppm Sacox by 57.8, 82.9, 89. 6 and 94. 3 % respectively.

Table 3 : Overview of daily feed intake and weight gain as well as total oocyst output during infection with E. intestinalis (trial 2)

Trial group	A	B	C	D	E	F
Feed intake g/d						
D-1 till D+5	111.7	117.6	115.7	106.2	118.7	106.3
	14.2	*26.0*	*15.7*	*8.9*	*15.5*	*15.2*
D+6 till D+11	113.3	54.0[a]	59.6	68.4	77.6[b]	82.6[b]
	36.7	*11.0*	*15.6*	*24.2*	*14.8*	*22.6*
D+12 till D+18	126.1	51.3	88.8	100.8	113.6	104.2
	21.8	*33.7*	*43.3*	*12.8*	*9.9*	*20.6*
Weight gain g/d						
D-1 till D+5	13.4	20.7	16.8	17.0	22.3	18.2
	41.8	*20.5*	*23.3*	*26.7*	*21.1*	*13.1*
D+6 till D+11	18.1	-35.0[a]	-24.3	-2.7[b]	-6.8[b]	10.7[b]
	36.3	*11.5*	*17.6*	*13.9*	*9.2*	*9.6*
D+12 till D+16	16.0	3.1	17.5	25.2	25.3	17.7
	40.5	*32.2*	*28.0*	*9.4*	*6.4*	*5.9*
Total oocyst output	2 060.8[1]	2 864 588.2[a]	1 207 891.6[b]	490 587.2[b]	298 555.3[b]	163 389.6[b]
(D+7 till D+16)	3 851.3	885 203.4	302 624.7	205 425.8	133 939.4	61 474.9
Reduction to B (%)		0.0	57.8	82.9	89.6	94.3

[ab] different superscripts are significantly different ($p<0.05$) ; [1] Identification of unsporulated oocysts contamination through adjacent infected animals

Values in italic letters refer to standard deviation of the mean.

Trial 3 : Infection with E. stiedai (Table 4)

Animals of group B (IC) showed a conspicuous loss of appetite and weakness during the critical phase which is characteristic for a distinct liver coccidiosis. All medicated groups were able to avoid largely this appearance. The response of group C (7.5 ppm Sacox) and D (15.0 ppm Sacox) did not follow a monotonous dose response relation regarding daily feed intake, weight gain and oocyst excretion. Due to the inverted dose efficacy relation, this data could not be validated. The medication with 22.5 and 30,0 ppm Sacox resulted in a significant higher feed intake as well as weight gain during the critical phase. In the prephase and recovering period, no differences occurred regarding these parameters. The total oocyst output was reduced significantly in both groups. Relative liver weights were 3.5, 5.8, 4.3, 3.9, 3.7 and 3.2 % for groups A/UC ; B/IC ; C, D, E, F. Data for groups E and F were significantly different from B/IC. The lesion score (liver) in the infected control of 3.2 was reduced to 1.9 and 2,0 in the 7.5 ppm and 15.0 ppm Sacox groups: the lesions in the 22.5 ppm and 30.0 ppm Sacox groups were markedly lowered to 0.7 and 0.3 respectively.

In conclusion, Sacox has proven to be very effective in dosages of 15.0 - 30.0 ppm in controlling intestinal coccidiosis caused by E. magna and E. intestinalis. The groups remained free of diarrhoea related to the massive reduction of oocysts. The small quantities of oocysts still excreted favoured the development of immunity followed by a superior weight gain development during the critical phase of the disease.

Under the conditions of severe E. stiedai infections, the Eimeria species responded best to dosages of 22.5 -30.0 ppm Sacox. These dosages prevented almost completely any liver lesion and completely hypertrophy of the liver. Focusing on field conditions, mixed infections of coccidia are predominant. According to our results and the experience from the field [VARGA (1982), VÖROS *et al.* (1984), SAMBETH (1986), NIEDZWIEDEK (1989)] a dosage of 20 - 25 ppm Sacox is recommended for the prevention of coccidiosis in fattening rabbits.

Table 4 : Overview of daily feed intake and weight gain as well as total oocyst output during infection with E. stiedai (trial 3)

Trial group	A	B	C	D	E	F
Feed intake g/d						
D-1 till D+4	121.1	121.4	133.4	105.8	103.8	103.1
	34.6	*21.6*	*25.0*	*14.7*	*38.4*	*18.6*
D+5 till D+16	112.9	67.1[a]	106.6	76.3	98.2b	112.5[b]
	32.5	*20.6*	*37.5*	*24.2*	*41.9*	*28.4*
D+17 till D+34	112.2	82.8	108.2	87.7	100.8	97.2
	31.3	*29.6*	*33.5*	*22.9*	*31.7*	*29.1*
Weight gain g/d						
D-1 till D+4	21.4	24.2	23.3	10.2	7.1	12.1
	28.0	*28.1*	*20.4*	*38.8*	*38.0*	*28.7*
D+5 till D+16	8.6	-14.8[a]	8.0	-1.7	9.0[b]	18.5[b]
	25.9	*12.2*	*19.9*	*12.7*	*15.4*	*11.6*
D+17 till D+34	12.7	15.4	14.9	9.9	10.7	6.1
	28.7	*5.9*	*2.5*	*12.1*	*4.8*	*9.8*
Total oocyst output	0.0	901 748.1[a]	50 713.1	168 278.2	82 000.6[b]	1 261.8[b]
(D+14 till D+34)		997 666.4	77 064.6	232 319.6	183 042.1	2 134.6
Reduction to B (%)		0.0	94.4	81.3	90.9	99.9

[ab] different superscripts are significantly different ($p<0.05$)
Values in italic letters refer to standard deviation of the mean.

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Zusammenfassung - In drei separaten Infektionsversuchen mit oraler Applikation von 5 x 10 Eimeria magna (Versuch 1), 5 x 10 Eimeria intestinalis (Versuch 2) oder 4 x 10 Eimeria stiedai (Versuch 3) pro Tier wurde die Dosis-Wirkungsbeziehung von 7,5 ; 15,0 ; 22,5 und 30,0 ppm Salinomycin-Natrium (Sacox, Hoechst AG) in männlichen Weißen Neuseeländern geprüft. Als Kontrolle dienten eine nicht infizierte, nicht medikierte und eine infizierte, nicht medikierte Versuchsgruppe. Während der kritischen Phase einer E. magna oder E. intestinalis Erkrankung zeigten 15,0 ; 22,5 und 30,0 ppm einen signifikant günstigen Einfluß auf Futteraufnahme und Gewichtszunahme im Vergleich zur infizierten, nicht medikierten Kontrolle. Die Gesamtoozystenausscheidung verringerte sich um 84,3 ; 92,9 bzw. 88,6 % im Versuch 1 und um 82,9 ; 89,6 bzw. 94,3 % im Versuch 2. Bezüglich der Infektion mit E. stiedai wirkten 22,5 und 30,0 ppm Sacox am besten. Beide Dosierungen verhinderten signifikant einen Rückgang der Futteraufnahme und der Gewichtszunahme. Das relative Lebergewicht (% der Körpermasse) von 5,8 % in der infizierten Kontrolle reduzierte sich signifikant auf 3,7 und 3,2 %, die Leberläsionen von 3,2 entsprechend auf 0,7 und 0,3.