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EFFECTS OF DIMETRIDAZOLE ON YOUNG RABBITS AFFECTED BY AN ACUTE DIGESTIVE DISORDER

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INTRODUCTION

Dimetridazole (8595 RP) or dimethyl-1,2 nitro-5 imidazole (DMZ) is a protozoa control drug developed by Rhône-Poulenc which also has antimicrobial properties, in particular as concerns gram-positive and anaerobic bacteria.

Because of its broad application, it is used on various animal species, in particular as prevention and treatment for histomoniasis and trichomoniasis in poultry and haemorrhagic enteritis in swine.

In rabbits, DMZ is used to control clostridial enterophathias and lambliasis, which makes it especially valid just after weaning when disequilibrium of the intestinal flora facilitates the development of pathogenic clostridia and lamblias *(giardia intestinalis)*.

Further, like in pigs and poultry, DMZ may well improve the productive performance of the rabbits.

DMZ is already being combined with other infection inhibitors in supplementary feeds provided to reared rabbits, in the field, although, in practice, its exact role has not been clearly defined.

That is why we sought to test different doses of DMZ on traditionally raised rabbits. We wanted to ensure that, at therapeutic rates the molecule was indeed harmless and to bring out its importance as a growth promoter in rabbits.

During our experiment, twice, but several months apart, the animals contracted a serious digestive disorder that we left untreated.

The origin of the disorder was more or less well defined, but apparently it could be traced to a variety of causes, which, in any case, had nothing to do with the product we were testing. We decided to carry out our experiment to completion, and draw lessons from the results, even if we could not fulfil our initial objective.

METHODS AND MATERIALS

The following design was used in both experiments:

Group	A	B	C	D
No. of rabbits	90	90	90	90
DMZ supplement (ppm)	0	100	200	400
Dosage in mg/kg lw/d	0	15	30	60

In other words there were 360 New Zealand rabbits (INRA 77 strain), weaned at the age of 28-30 days, and tatooed.

The fattening unit has constant ventilation, and droppings were removed every day on a conveyor belt. The animals were housed in flat-deck cages, 6 to a cage. The rabbits were not sex-selected, but were all of the same weight.

The test rabbits were kept in the central area of the fattening unit in order to avoid outside environmental effects.

The beginning of the test (D0) was the day of weaning. Diet A (control) was a "rabbit finishing diet", without a medical supplement. Diets B, C, and D were composed of the same basic feed, but were supplemented with 100, 200, and 400 ppm of DMZ, respectively. These diets were fed for three weeks as of the day of weaning (D0-D21). After D21, all the rabbits received the same diet as the control Group.

DMZ was fed as premixed Emtrymix (R) 300 Adrim, composed of:

- Dimetridazole (8595 RP) 300 g
- Maize flour *qsf* 1000 g

CONTROL MEASURES

Animals were weighed individually when entering the Group (D0), when the feeding regime was changed (D21), and at the end of the experiment (D49).

This was done to determine the average weight at weaning, in the middle of the fattening period, and at slaughter, and also the average daily weight gain per group and per period.

Feed distributed in the cages was first weighed in order to ascertain the average feed conversion ratio (FCR) per group, and per period.

Deaths were recorded, dead animals were weighed and examined by autopsy.

Feed analysis showed the following:

		Trial 1	Trial 2
Dry matter	(%)	87.8	91.3
Total crude protein	(%)	15.5	16.7
Raw fiber	(%)	14.9	14.5
Mineral matter	(%)	8.9	9.1

The DMZ content in the feed samples was as follows:

		Trial 1	Trial 2
Diet A (control)	(ppm)	0	0
Diet B	(ppm)	100	115
Diet C	(ppm)	194	196
Diet D	(ppm)	370	391

RESULTS AND DISCUSSION

Trial 1

Mortality (see Table no. 1)

This table shows the daily mortality figures, per treatment, from the beginning of the experiment (day 91 058) to slaughter (day 91 106).

All the dead animals, after autopsy, were put in three categories: typical caecal paresis, "enteritis", which included all the digestive disorders, and "miscellaneous", which included other causes of death and a few animals that were difficult to classify because of their state of decomposition.

Although the various analyses and investigations did not explain the precise cause of the caecal paresis syndrome, the feed used in this trial seem to have a direct effect. Further, the DMZ supplement had a completely, - seemingly beneficial - independent effect .

Aggregate mortality figures: the mortality rate decreased as the DMZ content in the diet increased, i.e.

84.8% in Group A - control group, no supplement
70.0% in Group B - 100 ppm supplement
63.3% in Group C - 200 ppm supplement
33.3% in Group D - 400 ppm supplement

These treatment-related differences seem to be significant, except for Groups B and C.

On the whole, the death rate in Group D (400 ppm DMZ) was about half that of Groups B and C and about one-third of the control group (no supplement).

Distribution of death occurrences

In all four treatments caecal paresis accounted for close to 50% of the deaths. But aside from the death incidence proper, it is worth noting the difference in the time of death. In Group A death occurred around D10 of the trial, in Groups B and C, 4 to 5 days later, and in Group D, 4 to 5 days after Groups B and C.

Performance (see Table no. 2)

Because of the high mortality rate, performance parameters are difficult to use, and must be interpreted with caution. That is why we have not tried to make a statistical analysis of the results.

But the following remarks seem valid:

- The weight of the rabbit at weaning (D0) was high (average of 712 g), and the four treatments were standardised.

- The liveweight of the surviving rabbits at D21 indicates a clear difference for Group A (1223 g), and also for Group B (1294 g) in comparison with Group C (1422 g) and, even moreso, Group D (1491 g).

- The final liveweight (D49) of the surviving rabbits shows that Group B almost made up for the difference in weight with Groups C and D, but that Group A remained lower than the other 3 groups (2465 g vs 2584 g for B, 2627 g for C, and 2596 g for D).

- The ADG, in rabbits that survived from D0 to D21 followed the same trend as for liveweight: 25.13 g (A), 28.49 (B), 34.04 (C) and 36.67 (D). Groups C and D were the only ones with "normal" figures.

- The ADG of animals that survived from D21 to D49 distinguishes A (36.81 g) from the three other groups: 41.35 g (B), 40.83 g (C), and 39.33 g (D).

The overall figures for ADG for rabbits that survived D0 to D49 confirms this trend: 37.56 g (A), 38.96 g (B), 40.09 g (C), and 39.06 g (D).

Figures on feed intake, by time period or for the total test period, cannot be interpreted, which also explains why the FCRs were not calculated.

Trial 2

Mortality (see Table no. 3)

This table shows the daily mortality figures, per treatment, from the beginning of the experiment (day 91 205) to slaughter (day 91 253).

All the dead animals, after autopsy, were put into three categories: caecal paresis, "enteritis" including digestive disorders, and "miscellaneous", which included other causes of death and a few animals that were difficult to classify because of their state of decomposition.

We related the high mortality rate we observed, regardless of treatment, to environmental problems that existed during the trial (extreme heat). Further, animals in Group A, during the first part of the trial, and all the animals after D21 received an unsupplemented diet (no general coccidian or infection control drugs), and no therapeutic care.

Overall mortality at D21, that is, at the end of the DMZ supplementation period as concerns Groups B, C, and D. In the control group (A) the mortality figure reached

50% between D10 and D21, while the other figures were: Group B 9%, Group C 5.5%, and Group D 3.3% during the first part of the fattening period.

The difference between A and the other three groups is very significant, and must be credited to the DMZ content.

It should also be pointed out that the mortality rates in Groups C and D were excellent, while in Group B it was fair, which suggest that a DMZ supplementation rate of 100 ppm is not high enough to fully control this type of cause of death.

The final mortality figure on D48 confirms the interim result: for the total experiment period, Group A had a mortality rate that was double the rate recorded for the three other, evenly affected, groups. The high mortality figures observed at the end, for all the groups, seems due to the problem of heat (see above). This explains why groups B, C, and D seemed, proportionately, most severely struck, since size, density, and liveweight per cage were much higher.

The distribution of death (Table no. 3) seems to prove that DMZ protects the digestive tracts of young rabbits, since paresis and enteritis observed in Group A appeared 10 days after weaning, and indeed corresponded to post-weaning digestive disorders connected to anaerobic pathogens of the intestinal flora.

Performance (see Table no. 4)

Because of the high mortality rate, performance parameters must be eyed with caution,and we did not make statistical tests on feed intake and FCRs. Furthermore, the analysis of variance on the growth criteria did not show any significant difference between treatment results, for any of the criteria.

The following observations and trends seemed valid, especially for the D0-D21 period during which Group B, C, and D rabbits consumed DMZ.

- On D0 (weaning) the average weight of the young rabbits in the groups was perfectly balanced : between 653 and 658 g.

- The liveweight of the surviving rabbits at D21 indicates a difference for Group A (1382 g), in comparison with Group B (1419 g), and, even moreso, with Group D (1427 g) and Group C (1447 g).

- The final liveweight (D48) confirms that on the average, Group A (2274 g) caught up with the other groups (2201 g, 2251 g, 2297 g). This compensatory growth in Group A can be explained by the low survival rates during the second half of the fattening period.

- The ADG in rabbits that survived from D0 to D21 followed the same trend as for liveweight: 34.97 g (A), 36.27 (B), 37.54 (C) and 36.91 (D). Results from Treatment A were clearly different from those of Treatments C and D; Treatment B gave in between results.

- The ADG for D21 to D48 and the overall ADG figures for D0 to D48 show that the growth performance levelled off in the four groups, which can be explained by the compensatory growth in Group A survivors and the mortality rates in the other three

groups. As overall figures, daily weight gains of 32.31 to 34.25 g is low, but they correspond to the usual growth figures during the hot summer period.

Figures on feed intake, and the FCR by time period or for the total test period, are very difficult to interpret. The rabbits were housed 6 to a cage, and feed was assigned to the number of animals present at weaning (i.e. 90 rabbits per group). With high mortality rates the intake figures were of no significance.

Hence the only worthwhile remark concerning Treatments B, C, and D, during the D0-D21 period is that the FCR seemed to improve slightly when DMZ was added to the diet (2.54 for B, 2.44 for C, and 2.37 for D).

On the whole, the average feed intake figures and the FCR are much the same for Groups B, C, and D: intake is slight and the FCR is high -- but should be considered in terms of mortality figures and the effect of the ambiant heat.

CONCLUSIONS

On two occasions, under the same experimental conditions, rabbits fed on a DMZ-enriched diet suffered a serious digestive disorder. Our observations are instructive for the following reasons:

- An analysis of mortality indicates that DMZ has a protective effect on the digestive tract of young rabbits with major digestive disorders (caecal paresis syndrome in Trial I and post-weaning enteritis in Trial II). In Trial I the mortality rate declined as the DMZ content in the diet increased, and, death did not occur systematically at the same time in each group. In Trial no. 2 the cause of the very high mortality rate in the control group seemed to be completely overcome in the groups fed a DMZ supplement during the three weeks of treatment, and protection improve as DMZ rates in the diet increased. The final mortality figures confirm the interim figures.

These observations confirm the effectiveness of DMZ on anaerobic bacteria, since this type of pathogenic flora is usually the one that develops in the intestinal syndrome.

- The performance analysis, (notwithstanding the caveats due to the high mortality rates), gives evidence of improved growth (liveweight and AWG) in the groups that received DMZ supplements, although there was no signficant difference between the treatments that could be statistically justified.

At the end of the day, under our experimental conditions, we can say that DMZ is not toxic for rabbits and that it is to be recommended, at a dose of 200 ppm, for the post-weaning period in order to prevent or control digestive disorders caused by anaerobia.

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ABSTRACT

During two fattening trials, twice 360 New Zealand rabbits were fed a diet supplemented with 0, 100, 200, and 400 ppm DMZ for a period of 3 weeks starting at weaning. We monitored the evolution of serious digestive disorders, of various origins, that were independent of the product being tested.

The mortality analysis showed that DMZ had a protective effect on the digestive tract: mortality seemed to be harnessed in rabbits fed a DMZ-supplemented diet, with protection improving as the DMZ content in the diet was increased.

The performance analysis provided no data to indicate a significant difference between treatments, but the groups that received DMZ supplements grew better.

We can purport that DMZ is not toxic for rabbits at the doses prescribed above, and that it can be used after weaning to prevent or fight digestive disorders resulting from the proliferation of anaerobic flora.

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Table no. 1 - MORTALITY FIGURES (Trial 1)

	Group A				Group B				Group C				Group D			
Date of death Year-day	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total
91 058																
91 061										1		1				
91 063						1		1								
91 068		2		2			2	2								
91 069	3	3		6		1		1	1	1		2				
91 070	3	5		8	1			1	1	1		2				
91 071	3	1		4	1	1		2	2	1		3		1		1
91 072		1		1		1		1	3	1		4	1			1
91 073	4	1		5	3	3		6	6	3		9				
91 074	4	1		5	2	4		6	2		1	3	1			1
91 075	2	3	2	7	2		3	5	4		5	9				
91 076	5	3		8	7	3	3	13	1	2	5	8	1		2	3
91 077	2	2		4	1	1		2	4		1	5	2	2		4
91 078	1	3		4	2	1	1	4					1	1		2
91 079	3	2		5	1	2		3			1	1	4	1		5
91 080	2	1		3		1		1		1		1	1			1
91 081	1	1		2		2		2			2	2				
91 082	2	3	2	7		1	1	2	1	1		2		3		3
91 083						2	1	3					1			1
91 084	1			1	1			1	1			1	1			1
91 085			2	2							2	2				
91 086			1	1			1	1								
91 087						2		2		1		1			1	1
91 088	1			1		2		2			1	1				
91 089							2	2								
91 091														1		1
91 092														2		2
91 098													1	1		2
91 105													1			1
91 106																
TOTAL	37	32	7	76 (84.4%)	21	28	14	63 (70%)	26	13	18	57 (63.3%)	15	12	3	30 (33.3%)

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Table no. 2 - PERFORMANCE (Trial 1)

	A			B			C			D			Total		
	N	$\bar{X}$	σ	N	$\bar{X}$	σ	N	$\bar{X}$	σ	N	$\bar{X}$	σ	N	$\bar{X}$	σ
Weight at weaning (D0) g	90	718	115	90	710	106	90	708	102	90	712	103	360	712	106
Weight at D21 (g)	31	1223	277	45	1294	292	44	1422	269	69	1491	229	189	1384	280
Final weight (D49) (g)	14	2465	217	27	2584	393	33	2627	249	60	2596	250	134	2587	282
A W G D0 - D21 (g)	31	25.13	15.04	45	28.49	12.53	44	34.04	11.51	69	36.67	8.49	189	32.21	12.20
A W G D21 - D49 (g)	14	36.81	7.58	27	41.35	7.66	33	40.83	5.47	60	39.33	6.35	134	39.84	6.63
A W G D0 - D49 (g)	14	37.56	4.21	27	38.96	7.55	33	40.09	4.11	60	39.06	4.64	134	39.14	5.20

Table no. 3 - MORTALITY FIGURES (Trial 2)

	Group A				Group B				Group C				Group D			
Date of death Year-day	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total	Caecal paresis	Enteritis	Other	Total
91 211										1		1				
91 213										2		2				
91 214														1		1
91 215	1	2		3	1			1								
91 216		4		4												
91 218	1	4	1	6		1		1								
91 219	3	1		4												
91 220		4	1	5												
91 221	2	5		7	1	3		4								
91 222		1		1	2			2								
91 223	2	2	1	5										1		1
91 224		1		1					2			2				
91 225		4		4												
91 226	2	3		5										1		1
TOTAL D21	11	31	3	45 (50%)	4	4		8 (9%)	2	3		5 (5.5%)		3		3 (3.3%)
91 227			1	1			2	2								
91 228			3	3												
91 229			1	1												
91 231									1	2		3				
91 232		1	1	2		1		1								
91 233											1	1			1	1
91 234		1		1		1		1						2		2
91 235						2		2		2		2		1		1
91 236									2	1		3		2		2
91 237		2		2												
91 238	1			1	1			1	1	5		6		2		2
91 239	1			1		3		3	1			1	2			2
91 240											3	3			2	2
91 241										1		1	3			3
91 242					2	1		3					2			2
91 243						1		1						2		2
91 244										1		1		2		2
91 246											1	1			1	1
91 248										1		1		1		1
91 249						1		1						1		1
91 250							1	1			1	1				
91 251														3		3
TOTAL D48	13	35	9	57 (63.3%)	7	14	3	24 (26.7%)	7	16	6	29 (32.2%)	7	19	4	30 (33.3%)

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Table no. 4 - PERFORMANCE (Trial 2)

	A			B			C			D			Total		
	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ	N	$\bar{x}$	σ
Weight at weaning (D0) g	90	658	79	90	653	81	90	657	77	90	656	80	360	656	79
Weight at D21 (g)	45	1382	208	82	1419	157	85	1447	135	87	1427	154	299	1424	160
Final weight (D48) (g)	33	2274	203	66	2201	303	61	2251	216	60	2297	237	220	2252	250
A W G D0 - D21 (g)	45	34.97	9.02	82	36.27	6.44	85	37.54	4.94	87	36.91	5.38	299	36.62	6.26
A W G D21 - D48 (g)	33	31.06	4.64	66	29.35	6.30	61	29.65	6.11	60	31.43	6.27	220	30.26	6.05
A W G D0 - D48 (g)	33	33.85	3.55	66	32.31	5.94	61	33.34	3.87	60	34.25	4.42	220	33.36	4.72
Feed intake D0 - D21 (g)	45	71.70	14.52	82	84.45	8.98	85	86.69	7.25	87	85.24	7.94	299	82.02	11.55
Feed intake D21 - D48 (g)	33	108.64	41.68	66	116.04	9.83	61	113.05	12.87	60	114.83	16.59	220	113.30	22.48
Feed intake D0 - D48 (g)	33	84.33	34.52	66	102.22	5.80	61	101.52	8.46	60	101.89	11.86	220	97.49	20.00
F C R D0 - D21	45	4.69	4.07	82	2.54	0.37	85	2.44	0.20	87	2.37	0.23	299	3.01	2.23
F C R D21 - D48	33	3.71	0.73	66	3.60	0.51	61	3.63	0.52	60	3.72	0.56	220	3.66	0.57
F C R D0 - D48	33	3.37	1.12	66	3.60	0.51	61	3.63	0.52	60	3.72	0.56	220	3.58	0.72