

EFFECT OF NORFLOXACIN NICOTINATE ON THE PERFORMANCE AND FAECAL FLORA OF GROWING RABBITS

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Abstract - In a tolerance trial 2 x 6, 6-10 weeks old New Zealand White growing rabbits were treated with 2 x 7 mg/kg b.w./day (Group 1) and with 2 x 21 mg/kg b.w./day (Group 2) norfloxacin nicotinate via drinking water for 5 days. Six rabbits of Group 3 served for control animals.

There were no significant differences between average daily weight gain of treated and control groups any part of 28 day trials. Feed intake of rabbits of Group 1 was higher significantly than that of animals of control group but the feed conversion ratios did not differ from each other significantly. Mainly the dose of 2 x 21 mg/kg b.w./day decreased daily water intake, but the differences were not significant. Treatment with norfloxacin nicotinate did not influence the composition of rabbit faecal flora. Only the coliform bacteria disappeared from the flora immediately after treatment but two weeks after it these bacteria were also detectable in faeces.

In a prophylactic experiment 2 x 30, 40 ±2 days old New Zealand White rabbit were treated with 2 x 7 mg/kg b.w./day (Group 1) and 20 mg/kg b.w./day (Group 2) norfloxacin nicotinate via drinking water for 3 days. 30 rabbits in the same age and weight formed the untreated control group.

Rabbits of treated groups gained better in the first two weeks of experiment and results relating to the whole experiment were the same, but differences were not significant. Feed conversion ratio of treated groups were favourable in the first two weeks of experiment than that of control group. In case of the group 1 F.C.R. differed significantly from F.C.R. of control group but regarding to whole experiment they did not differ significantly. Mortality of all groups were low the highest mortality rate was observed in the control group.

INTRODUCTION

Growing rabbits, mainly after weaning, often threatened by enteric diseases (1, 10). Etiology of these diseases is multifactorial and in the field regularly two, three or more causative agents are present at the same time (10, 16).

For prevention or treatment of these diseases several antibiotics, coccidiostats, probiotics have been used (4, 7, 9, 12, 14, 15). Some of them, mainly in per oral application, are more or less toxic for rabbits (6, 10, 11, 13, 15). Most of these antibiotics influence the bacterial flora of small and large intestines and more or less alter it (12, 15).

Fluoroquinolones (gyrase inhibitors) are broad-spectrum antiinfectives which are suitable for the treatment of several bacterial diseases of animals. Enrofloxacin a member of this group is well tolerated by rabbits (15) and it proved to be very effective against enteropathogenic *Escherichia coli* of rabbits (9).

Norfloxacin is a relatively new member of this group with more or less the same characteristics than that of enrofloxacin. The aim of this study was to investigate tolerance of rabbits to norfloxacin and to evaluate effect of it on performance and mortality of growing rabbits after weaning.

MATERIAL AND METHODS

In the first (tolerance) test 18, six weeks old New Zealand White rabbit were divided into 3 groups. The average weight of group were 1602, 1603 and 1611 g respectively. All groups consisted of 3 females and 3 males. Rabbits of the Group 1 were treated with 2 x 7 mg/kg b.w./ day, animals of Group 2 were given 2 x 21 mg/kg b.w./day norfloxacin nicotinate via drinking water for the first 5 days of 28 days long experiment. Rabbits of Group 3 served as control animals. All rabbits were individually caged.

Weight of animals and amount of consumed feed were weighted on the 16th and 28th day of trial while water intake of rabbits was checked daily. At the same time clinical examinations were performed.

Composition a faecal flora was determined immediately before (on the 1st day) and after (on the 6 day) the norfloxacin treatment and on the 20th day of experiment. The bacteriological examinations were carried out basically by method of BRAUN *et al.* (1966) but this method was modified by VÖRÖS (19). Modifications

were follows: anaerobic cultivation was done in AnaeroJar with AnaeroGen (Oxoid) and for counting clostridia Wilson-Thompson-Blair media was used.

In the second experiment of 90, 40 ± 2 days old New Zealand White rabbits caged individually 3 groups were formed (average weight of them were 1167, 1171 and 1166 g respectively). Animals of Group 1 (30 rabbits) were treated with 2 x 7 mg/kg b.w./day, 30 rabbits of Group 2 with 20 mg/kg b.w./day norfloxacin nicotinate via drinking water for 3 days at the beginning of trial. 30 rabbits formed the untreated control group (Group 3). Total length of trial was 5 weeks. All rabbits were fed with Puristar rabbit pellet (Purina-Hage Rt. Hungary). Weight and feed intake of rabbits were checked on the 14th and 35th day of experiment. Mortality was recorded and post-mortem examination was done every time. From liver, spleen, kidney and caecum of carcasses routine bacteriological examination was done by the help of 5 % sheep blood agar and McCONKEY agar incubated aerobically.

Performance data of both experiments were evaluated statistically by Student t-test.

RESULTS

Results of weight gain of rabbits treated with 2 x 7 mg/kg b.w./day and with 2 x 21 mg/kg b.w./day norfloxacin nicotinate and control animals were summarised in table 1.

Table 1 : Weight gain of rabbits treated with norfloxacin nicotinate tolerance test

Treatment	Average daily weight gain (g)		
	1 - 16.	17 - 28.	1 - 28. days
norfloxacin nicotinate			
2 x 7 mg/kg b.w./day	33.3 ± 4.0 ^a	24.1 ± 11.4 ^a	29.3 ± 5.2 ^a
2 x 21 mg/kg b.w./day	28.1 ± 3.7 ^a	27.4 ± 8.7 ^a	27.8 ± 4.5 ^a
control	29.7 ± 5.7 ^a	23.7 ± 3.8 ^a	27.2 ± 5.2 ^a

a, b, c - different letters in the same column mean significant difference

The lower, more or less therapeutic dose, not significantly increased the weight gain of rabbits in the first period of trial. Regarding to the whole experiment both treated groups gained not significantly better than animals of control group.

Rabbits of Group 1 consumed significantly more feed than animals of control group and not significantly more than rabbits of Group 2 between 1-16 days of experiment (Table 2.). Difference between values of Group 1 and Group 3 proved to be significant for the whole time of experiment.

Table 2 : Feed intake of rabbits treated with norfloxacin nicotinate tolerance test

Treatment	Average feed intake (g)		
	1 - 16.	17 - 28.	1 - 28. days
norfloxacin nicotinate			
2 x 7 mg/kg b.w./day	2192 ± 138 ^b	1778 ± 252 ^a	3970 ± 285 ^b
2 x 21 mg/kg b.w./day	1942 ± 105 ^{ab}	1686 ± 341 ^a	3628 ± 400 ^{ab}
control	1830 ± 126 ^a	1637 ± 234 ^a	3450 ± 343 ^a

a, b, c - different letters in the same column mean significant difference

Table 3 : Feed conversion ratio of rabbits treated with norfloxacin nicotinate tolerance test

Treatment	Average feed conversion ratio		
	1 - 16.	17 - 28.	1 - 28. days
norfloxacin nicotinate			
2 x 7 mg/kg b.w./day	4.15 ± 0.47 ^a	5.54 ± 0.94 ^a	4.59 ± 0.17 ^a
2 x 21 mg/kg b.w./day	4.36 ± 0.50 ^a	5.45 ± 1.34 ^a	4.72 ± 0.60 ^a
--- (control)	3.98 ± 0.88 ^a	5.79 ± 0.54 ^a	4.63 ± 0.79 ^a

a, b, c - different letters in the same column mean significant difference

There were no significant differences between feed conversion ratio of Group 1, 2 and 3 any part of experiment (Table 3).

Table 4 : Water consumption of rabbits treated with norfloxacin nicotinate tolerance test

Treatment	Average water consumption (ml/day)	
norfloxacin nicotinate	1 - 16.	17 - 28. days
2 x 7 mg/kg b.w./day	238 ± 32 ^a	268 ± 36 ^a
2 x 21 mg/kg b.w./day	227 ± 54 ^a	256 ± 32 ^a
control	245 ± 44 ^a	286 ± 48 ^a

a, b, c - different letters in the same column mean significant difference

Norfloxacin nicotinate, mainly in higher dose decreased water consumption of rabbits comparing to that of control animals in the first and second part of experiment (Table 4) Differences were not significant.

Of 18 rabbits involved to tolerance experiment, 1 rabbit died from the control group owing to rhinitis and pneumonia. From lungs *Pasteurella multocida* was isolated in pure culture.

Neither 2 x 7 mg/kg b.w./day nor 2 x 21 mg/kg b.w./day norfloxacin dose influenced composition of faecal bacteria flora to much degree (Table 5. 6. 7.) Only the coliforms disappeared from faecal flora after norfloxacin treatment. Two weeks after treatment coliforms also appeared in faecal flora of rabbits consumed lower dose norfloxacin. Treatments did not influence ratio of coccus, lactobacillus and bacteroides in the faeces in the investigated time. Number of bacillus became more with several percentages when coliforms disappeared from the flora.

Table 5 : Effect of norfloxacin nicotinate treatment on the composition of faecal flora of rabbits Examination before treatment

Treatment	Total aerobic count, No/g	Bacillus No/g, %*	Coccus No/g, %*	Colif. No/g, %*	Total anaerobic count, No/g	Lacto-bacillus No/g, %**	Bacteroides No/g, %**	Clostridium, No/g %**
2x7 mg/kg	1.76 x 10 ⁶	1.34 x 10 ⁶ 76	1.31 x 10 ⁵ 8	2.83 x 10 ⁵ 16	5.56 x 10 ⁵	4.90 x 10 ⁵ 88	6.66 x 10 ⁷ 12	2.60 x 10 ²
2x21 mg/kg	3.30 x 10 ⁶	3.02 x 10 ⁶ 91	1.48 x 10 ⁵ 5	1.02 x 10 ⁵ 3	2.08 x 10 ⁸	1.81 x 10 ⁸ 87	2.76 x 10 ⁷ 13	2.0 x 10 ²
Control	1.83 x 10 ⁷	1.23 x 10 ⁷ 89	7.55 x 10 ⁵ 6	7.38 x 10 ⁵ 5	4.22 x 10 ⁸	3.80 x 10 ⁸ 90	4.00 x 10 ⁷ 10	4.10 x 10 ³

* in the % of total aerobic count

** in the % of total anaerobic count

Every values of the table is the average of 3 samples

Table 6 : Effect of norfloxacin nicotinate treatment on the composition of faecal flora of rabbits Examination after treatment

Treatment	Total aerobic count, No/g	Bacillus No/g, %*	Coccus No/g, %*	Colif. No/g, %*	Total anaerobic count, No/g	Lacto-bacillus No/g, %**	Bacteroides No/g, %**	Clostridium, No/g %**
2x7 mg/kg	4.78 x 10 ⁶	4.54 x 10 ⁶ 95	2.40 x 10 ⁵ 5	0	5.42 x 10 ⁸	4.88 x 10 ⁸ 90	5.33 x 10 ⁷ 10	5.33 x 10 ²
12x21 mg/kg	7.25 x 10 ⁶	6.85 x 10 ⁶ 95	1.48 x 10 ⁵ 5	0	8.62 x 10 ⁸	7.50 x 10 ⁸ 87	1.12 x 10 ⁸ 13	3.33 x 10 ¹
Control	2.58 x 10 ⁶	2.30 x 10 ⁶ 89	1.66 x 10 ⁵ 7	1.08 x 10 ⁵ 4	3.24 x 10 ⁸	2.79 x 10 ⁸ 86	4.53 x 10 ⁷ 14	3.33 x 10 ²

* in the % of total aerobic count

** in the % of total anaerobic count

Every values of the table is the average of 3 samples

**Table 7.: Effect of norfloxacin nicotinate treatment on the composition of faecal flora of rabbits
Examination two weeks after treatment**

Treatment	Total aerobic count, No/g	Bacillus No/g, %*	Coccus No/g, %*	Colif. No/g, %*	Total anaerobic count, No/g	Lacto-bacillus No/g, %**	Bacteroides No/g, %**	Clostridium, No/g %**
2x7 mg/kg	3.98 x 10 ⁶	3.43 x 10 ⁶ 86	2.65 x 10 ⁵ 7	2.59 x 10 ⁵ 7	6.72 x 10 ⁸	6.02 x 10 ⁸ 90	7.00 x 10 ⁷ 10	1.67 x 10 ²
2x21 mg/kg	1.75 x 10 ⁶	1.66 x 10 ⁶ 95	8.78 x 10 ⁴ 5	0	2.02 x 10 ⁸	1.82 x 10 ⁸ 90	2.00 x 10 ⁷ 10	2.0 x 10 ²
Control	5.38 x 10 ⁶	4.79 x 10 ⁶ 89	2.62 x 10 ⁵ 5	3.15 x 10 ⁵ 6	2.66 x 10 ⁸	2.33 x 10 ⁸ 88	3.30 x 10 ⁷ 12	3.00 x 10 ²

* in the % of total aerobic count

** in the % of total anaerobic count

Every values of the table is the average of 3 samples

Table 8 : Weight gain of rabbits treated with norfloxacin nicotinate for prophylactic purpose

Group	Norfloxacin nicotinate dose	Average daily weight gain (g)		
	mg/kg b.w./day	1 - 14.	15 - 35.	1 - 35. days
1.	2 x 7	42.7 ± 6.0 ^a	30.1 ± 4.8 ^a	35.1 ± 4.0 ^a
2.	20	41.5 ± 8.3 ^a	33.5 ± 4.5 ^a	36.3 ± 4.6 ^a
3.	Control	38.0 ± 7.0 ^a	34.3 ± 4.0 ^a	34.6 ± 5.3 ^a

a, b, c - different letters in the same column mean significant difference

Rabbits of both norfloxacin treated groups gained not significantly better than rabbits of the untreated control group in the first two weeks of experiment (Table 8.). Results of the treated groups relating to the whole trial were also not significantly better than that of control group. Rabbits of Group 2 had the highest weight gain for the whole experiment.

Table 9 : Feed intake of rabbits treated with norfloxacin nicotinate for prophylactic purpose

Group	Norfloxacin nicotinate dose	Average feed intake (g)		
	mg/kg b.w./day	1 - 14.	15 - 35.	1 - 35. days
1.	2 x 7	2161 ± 210 ^a	3524 ± 281 ^a	5685 ± 491 ^a
2.	20	2158 ± 253 ^a	3836 ± 478 ^a	5994 ± 732 ^a
3.	Control	2127 ± 263 ^a	3484 ± 388 ^a	5611 ± 651 ^a

a, b, c - different letters in the same column mean significant difference

Feed intake of rabbits of different groups did not differ from each other significantly (Table 9.) Relating to the whole experiment animals of Group 2 consumed the most amount feed.

Table 10 : Feed conversion ratio of rabbits treated with norfloxacin nicotinate for prophylactic purpose

Group	Norfloxacin nicotinate dose	Average feed conversion ratio		
	mg/kg b.w./day	1 - 14.	15 - 35.	1 - 35. days
1.	2 x 7	3.75 ± 0.36 ^a	5.60 ± 0.87 ^a	4.71 ± 0.48 ^a
2.	20	3.84 ± 0.47 ^{ab}	5.36 ± 0.69 ^{ab}	4.58 ± 0.39 ^a
3.	Control	4.20 ± 0.67 ^b	4.84 ± 0.60 ^b	4.56 ± 0.45 ^a

a, b, c - different letters in the same column mean significant difference

In the first part of experiment feed conversion ratio of rabbits of Group 1 was significantly more favourable than that of animals of control group and not significantly better than that of rabbits treated with 20 mg/kg b.w./day norfloxacin for 3 days (Table 10.). Between 15-35 days however feed conversion ratio of control group was significantly better than F.C.R. of rabbits treated with 2 x 7 mg/kg b.w./day norfloxacin nicotinate. Relating to the whole experiment feed conversion ratios of Group 1, 2 and 3 did not differ from each other significantly.

Table 11 : Mortality of rabbits treated with norfloxacin nicotinate for prophylactic purpose

Group	Norfloxacin nicotinate dose mg/kg b.w./day	Mortality		
		1 - 14.	15 - 35.	1 - 35. days
1.	2 x 7	0	1	1
2.	20	1	2	3
3.	Control	2	3	5

Mortality of all groups were very low (Table 11) Losses of treated groups were especially low comparing to losses of control group. Except of one rabbit from the control group all rabbits died owing to enteric diseases. In this carcasses the post mortem examinations revealed full packed stomach, enteritis in small intestines and haemorrhagies in the wall of caeca which contain were fluid with gas. of 8 carcasses from 6 caeca *Escherichia coli* were isolated in great number and from 4 died rabbits clostridia were isolated 10^3 - 10^4 number. One rabbit suffered pneumonia and from its lungs *Pasteurella multocida* was isolated.

DISCUSSION

In the tolerance test both dose (2 x 7 and 2 x 21 mg/kg b.w./day) norfloxacin nicotinate not significantly increased the weight gain of rabbits and improved feed conversion ratio of them. These findings are accordance with Peters *et al.* (1991) and VÖRÖS (1995) results which they got with enrofloxacin. Norfloxacin like enrofloxacin in higher than therapeutic dose not significantly decreased the water consumption of rabbits (VÖRÖS, 1995)

Five days norfloxacin treatment did not influenced significantly the composition of faecal flora. Only coliforms disappeared from the faeces and proportion of bacilli increased in a small degree. This finding is very similar to results of faecal flora examination in enrofloxacin treated rabbits (VÖRÖS, 1995).

In the second, efficacy test rabbits treated with 2 x 7 and 20 mg/kg b.w./day norfloxacin via drinking water gained not significantly better than animals of control group. These results are very similar to results of enrofloxacin treated rabbits in two Belgian commercial rabbitries (PEETERS *et al.*, 1991). Regarding to the whole experiment feed intake and feed conversion ratio of rabbits of treated and control groups not differ from each other significantly. Mortality of norfloxacin treated rabbits was lower than mortality of control group, but the very low mortality of all groups do not allow to conclude that norfloxacin decreases the mortality of young rabbits.

Norfloxacin nicotinate is well tolerated after oral administration by growing rabbits. At the same time norfloxacin increases the weight gain, improves the feed conversion ratio and probably decreases mortality of young rabbits.

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Die Wirkung von Norfloxacin Nicotinate auf die Leistung und Darmkotflora der Jungkaninchen

- In einem Toleranzversuch wurden 2x6, 6-10 Wochen alte Jungkaninchen (Rasse: Neuseeländer Weiss) mit Norfloxacin Nicotinate in Dosen von 2x7 mg/kg Körpermasse/Tag (Gruppe 1) und 2x21 mg/kg Körpermasse/Tag (Gruppe 2) durch Trinkwasser 5 Tagen lang behandelt. Die Kontrollgruppe (Gruppe 3) bestand aus 6 Kaninchen. Es gaben keine signifikante Unterschiede zwischen den durchschnittlichen täglichen Massenzuwachs der Versuchs- und Kontrolltieren während des 28-tägigen Versuchsperiod. Die Futteraufnahme von den Kaninchen in der Gruppe 1 war signifikant grösser als von den in der Kontrollgruppe, aber der Anteil der Futtertransformation unterschied sich nicht voneinander. Hauptsächlich die Dosis von 2x21 mg/kg Körpermasse/Tag verringerte die tägliche Wasseraufnahme, aber die Unterschiede waren nicht signifikant.

Die Behandlung mit Norfloxacin Nicotinate hatte keine Wirkung auf die Darmflora. Nur die Coliform Bakterien verschwanden aus der Flora bald nach der Behandlung, aber in 2 Wochen waren sie wieder im Kot nachweisbar.

In einem prophylaxischen Versuch wurde 2x30, 40+2 Tagen-alte Kaninchen (Rasse: Neuseeländer Weiss) mit Norfloxacin Nicotinate in den Dosen von 2x7 mg (Gruppe 1) und 20 mg/kg Körpermasse/Tag (Gruppe 2) durch Trinkwasser 3 Tagen lang behandelt. Die unbehandelte Kontrollgruppe bestand aus 30 Kaninchen gleiches Alters und gleicher Körpermasse.

Die Kaninchen in den behandelten Gruppen zunahmen intensiver in den ersten Wochen des Experiments und die Ergebnisse in Bezug auf den ganzen Versuch waren gleich, die Unterschiede waren nicht signifikant. Der Anteil der Futtertransformation in den behandelten Gruppen war günstiger in den ersten 2 Wochen des Versuches als in der Kontrollgruppe. Die Futtertransformation-Rate der Gruppe 1 unterschied sich signifikant von der in der Kontrollgruppe, aber bezüglich des ganzen Versuches diese Werte zeigten keine Unterschiede. Die Mortalität in allen Gruppen war niedrig, die höchste Mortalität-ziffer war in der Kontrollgruppe festgestellt.
