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On the efficacy, innocuity and residual depletion of flavomycin in confined steers

Avaliação da eficácia, inocuidade e depleção residual da flavomicina em novilhos confinados

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Abstract
Flavomycin is a non-ionophore additive little studied in finishing confined cattle. Therefore, this study aimed to evaluate the effectiveness of flavomycin on productive performance, ingestive behavior, carcass traits and biochemical parameters of steers finished in confinement. 32 whole steers, ½ Angus e ½ Nellore blood, from the same herd, with a mean age of 11 ± 1.5 months and initial body weight of 337 ± 6 kg were evaluated. The experiment was a randomized block design, consisting of two treatments and eight replications, as follows: Diet without flavomycin (control) and Diet with flavomycin (0.5 g FLAVIMPEX®80 animal day^{-1}). There was no difference between treatments, the average dry matter intake of the animals was 10.03 kg day^{-1}, feed efficiency was 0.158 kg, average daily gain was 1.593 kg day^{-1}, apparent diet digestibility was 61.69%. The use of flavomycin was not effective in animal performance, and caused no changes in ingestive behavior and carcass traits of the animals. Total Plasma Protein, Aspartate amino-transferase and creatinine were lower for animals supplemented with flavomycin compared to the control group. In relation to the experimental period, there was a reduction in the levels of Total Plasma Protein, an increase in albumin, Gamma-Glutamyl Transferase and urea in cattle, but all remained within the reference range for the species.
Keywords: Animal performance; Biochemical markers; Food additive; Ingestive behavior.

Resumo
A flavomicina é um aditivo que pertence à classe dos não ionóforos, contudo, com poucos estudos realizados com bovinos confinados em fase de terminação. Diante disso, o objetivo do presente estudo foi avaliar a eficácia da flavomicina sobre o desempenho produtivo, comportamento ingestivo, características de carcaça e os parâmetros bioquímicos de novilhos terminados em confinamento. Foram avaliados 32 novilhos inteiros, ½ sangue Angus ½ sangue Nelore, provenientes do mesmo rebanho, com idade média de 11 meses ± 1,5 meses e peso corporal inicial de 337 kg ± 6 kg. O delineamento experimental foi o de blocos casualizados, composto por dois tratamentos e oito repetições, sendo: Dieta sem flavomicina (controle) e Dieta com flavomicina (0,5 g animal dia^{-1} do produto FLAVIMPEX®80). Não ocorrendo diferença entre os tratamentos, o consumo de matéria seca médio dos animais foi de 10,03 kg dia^{-1}, eficiência alimentar de 0,158 kg, ganho médio diário de 1,593 kg dia^{-1}, digestibilidade aparente da dieta de 61,69%. O uso da flavomicina não foi eficaz no desempenho animal, assim como não trouxe alterações no comportamento ingestivo e melhorias nas características de carcaça dos animais. A Proteína Plasmática Total, Aspartato amino-transferase e creatinina foram inferiores para os animais suplementados com flavomicina em relação ao grupo controle. Em relação ao período experimental houve redução nos índices de Proteína Plasmática Total, aumento na albumina, Gama-Glutamil Transferase e ureia dos bovinos, mas todos se mantiveram dentro dos valores de referência para a espécie.
Palavras-chave: Aditivo alimentar; Comportamento ingestivo; Desempenho animal; Marcadores bioquímicos.

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Introduction

The increase in the cost of animal feed strongly indicates the need to seek improvements in the productive efficiency of animals. Aiming at this maximization, understanding the real action that different rumen microorganisms have on food digestion and employing techniques that promote changes in their activities, to achieve improvements in the efficiency of use of dietary nutrients, have been carried out by researchers[1]. A technique used and accepted among farmers is the use of rumen fermentation modulators.

Rumen fermentation modulators are used as an important tool to promote an increase in animal growth, digestibility and efficiency in the use of dietary nutrients, resulting in greater profitability for finishing systems[2,3]. However, due to restrictions imposed on the use of antibiotics in animal feed, it is necessary to produce non-drug additives, that is, without pharmaceutical agents[4].

According to Tae-Il et al. [5], in the current market there is a range of food additives available, including flavomycin, which is a growth promoter, but with little information available. Flavomycin (bambermycin) is a non-ionophore additive that prevents peptidoglycan synthesis in the bacterial cell wall[6]. This additive can still bring indirect benefits, suppressing pathogenic Gram-negative bacteria[7], as well as stimulating Gram-positive bacteria, in addition to promoting a higher molar proportion of propionate in the rumen[8].

Flavomycin acts mainly in the intestine against *Fusobacterium necrophorum*, and opportunistic pathogenic bacteria, which generate a reduction in protein turnover in the intestinal wall. After suppression of these bacteria, there is greater availability of amino acids for the animal, which can improve productive performance[9].

Although flavomycin is considered a safe additive in ruminant feed, there are few data available in the literature, especially considering forage-based diets. In view of the above, the present study aimed to evaluate the productive performance, ingestive behavior, post-slaughter carcass traits and serum parameters of steers finished in confinement receiving flavomycin in the diet.

Material and methods

The experiment was carried out at the Animal Production Center (NUPRAN), Universidade Estadual do Centro-Oeste (UNICENTRO), located in Guarapuava, state of Paraná. The experimental procedures were previously submitted to the Animal Research Ethics Committee (CEUA/UNICENTRO), and approved for execution under the official letter 004/2015.

Thirty-two ½ Angus e ½ Nellore blood, with an average initial weight of 337 ± 6 kg, and an average age of 11 ± 1.5 months, were previously dewormed with a 5% levamisole hydrochloride-based anthelmintic, at a dose of 5mg levamisole hydrochloride per kg body weight. (Zoetis, Campinas – SP, Brazil). The experimental design was randomized blocks, consisting of two treatments: Diet without flavomycin (control) and Diet with flavomycin (0.5 g FLAVIMPEX® 80 animal day^{-1}, sufficient amount to provide 40 mg flavomycin), (Impextraco Latin America, Curitiba – PR, Brazil).

Each treatment consisted of eight replicates, with each replicate corresponding to a pen with two animals. The facilities consisted of 18 feedlot pens, with an area of 15 m^2 each (2.5 m x 6.0 m). Each pen had a concrete feeder measuring 2.30 m in length, 0.60 m in width and 0.35 m in height and an automatic metal water trough. The experiment lasted 115 days, with 10 days for adaptation of the animals to the diets and facilities and 105 days for data collection. The diets consisted of corn silage at a constant ratio of 50% forage to 50% concentrate, on a dry matter basis, provided *ad libitum*.

Feeding was performed twice a day, at 06:30 am and 05:00 pm, with voluntary feed intake recorded daily by weighing the amount offered and leftovers from the previous day. The supply was adjusted daily, considering 5% leftovers of the dry matter offered in relation to the amount consumed. Food was provided as total mixed ration (TMR); Flavomycin was provided individually on the TMR, in order to guarantee the ingestion of the product by the animals. The concentrate was prepared with soybean meal: 5.1%; soybean hulls: 7.0%; wheat bran: 20.0%; ground barley grain: 8.3%; barley rootlet: 7.3%; ground corn kernels: 33.7%; Corn germ: 6.7%; calcitic limestone: 3.9%; peanut meal: 5.0%; common salt: 0.6%; livestock urea: 1.7%; and mineral vitamin premix: 0.7%.

Homogeneous samples of silage and concentrate were dried in a forced ventilation oven at 55°C for 72 hours to determine the partially dry matter. The pre-dried samples were ground in a Wiley mill with a 1 mm mesh sieve and analyzed for the contents of dry matter (DM), mineral matter (MM) by incineration at 550ºC (4 hours), crude protein (CP) by the micro Kjeldahl method, according to techniques described in the AOAC (10). Neutral detergent fiber (NDF) content was obtained according to Van Soest *et al*.[11] with heat-stable α-amylase and acid detergent fiber (ADF), according to Goering & Van Soest[12]. Acid detergent lignin (ADL) content was determined by following the methodology described by Silva and Queiroz[13]. Total digestible nutrients (TDN) content was calculated according to equations proposed by Bolsen *et al*.[14].

Equation 1: TDN,% =87.84-(0.70*ADF)

To determine the total dry matter, samples were taken to an oven at 105ºC for 16 hours[13] and to determine the P and Ca contents, analyses were performed according to the methodology described by Tedesco *et al*.[15] as

shown in Table 1.

Table 1. Chemical composition of foods supplied to animals and average values of the experimental diet, on a total dry matter basis

Parameters	Corn Silage	Concentrate	Experimental Diet
Dry matter, %	31.58	89.59	60.59
Mineral matter, % DM	2.24	9.68	6.02
Crude protein, % DM	5.66	21.33	13.54
Neutral detergent fiber, % DM	43.86	29.31	41.47
Acid detergent fiber, % DM	23.48	13.41	22.10
Total digestible nutrients, %	71.40	78.45	72.37
Ca, %	0.13	1.67	0.90
P, %	0.18	0.58	0.38

Guarantee level of the premix per kg concentrate: vit. A: 16,000 IU; vit D3: 2,000 IU; vit. E: 25 IU; S: 0.36 g; Mg: 0.74 g; Na: 3.6 g; Co: 0.52 mg; Cu: 22.01 mg; F: 18.00 mg; I: 1.07 mg; Mn: 72.80 mg; Se: 0.64 mg; and Zn: 95.20 mg.

Performance was evaluated by weighing the animals individually, on the first experimental day, day 0, and on the subsequent days, 28, 56, 84 and 105 days. Animals were fasted from solids for 12 hours and individually weighed on a digital scale, coupled to a Romancini squeeze chute. Variables evaluated were body weight (BW), average dry matter intake, expressed in kg animal day^{-1} (ADMI) according to equation 2, average dry matter intake, expressed as percentage of body weight (ADMI, % BW) according to equation 3, average daily weight gain (ADG, kg day^{-1}), according to equation 4 and feed efficiency (FE, kg kg^{-1}) according to equation 5.

Equation 2: ADMI = ADMITotal provided – total leftover food from the previous day.

$$\text{Equation 3: } ADMI = \left(\frac{ADMI}{BW}\right) * 100$$

$$\text{Equation 4: } ADG = \left(\frac{BW_f - BW_i}{105}\right) * 100$$

where: $BW_{f:}$ body weight at the end of the period; $BW_{i:}$ body weight at the beginning of the period.

$$\text{Equation 5: } FE = \left(\frac{ADG}{ADMI}\right)$$

The ingestive behavior of the animals was performed in a continuous time of 48 hours, on days 57, 58 and 59 of the experimental period. This evaluation started at 12 noon on the first day and ended at 12 noon on the third day. Observations were made by 9 observers per shift, in a rotation system every 6 hours. Readings were taken at regular 3-minute intervals. Animal behavior data, represented by idling, ruminating, water drinking and feeding, were expressed in hours day^{-1}. On the same occasion, the frequency of the occurrence of feeding, watering, urination and defecation activities, expressed in number of times per day, were also recorded, following the same methodology. In the night observation, the environment was kept under artificial lighting, a condition held since the arrival of the animals.

The apparent digestibility of the diet was evaluated by determining the dry matter digestibility (DMD), for which the total collection of feces from each experimental unit was performed at the end of each shift, with the aid of scrapers, for two consecutive days, and to avoid interference from dirt, pens were washed to remove any and all impurity could interfere with the collection. Feces were weighed and sampled at each 6-hour shift, and then stored in a freezer at -18ºC until analysis. After the end of the evaluation, samples were thawed, homogenized to form a composite sample, corresponding to each experimental unit. The DM of food, leftovers and feces from each experimental unit were determined using the same procedures adopted for food analysis. Thus, the apparent digestibility of DM was calculated using equation 6.

Equation 6:

$$AD(\%) = \left(\frac{DM_{ingested} - DM_{excreted}}{DM_{ingested}}\right) * 100$$

On experimental days 0, 28, 56 and 84, blood samples were drawn from animals in each pen through the coccygeal vein. With the aid of a syringe and needle, 15 mL blood was drawn from each animal, 5 mL of which were stored in a tube with EDTA for quantification of fibrinogen and total plasma protein (TP) and the other 10 mL were stored in a tube without EDTA for quantification of gamma-glutamyltransferase (GGT) and aspartate aminotransferase (AST) enzymes, albumin, urea and creatinine.

Samples with EDTA, after collection, were used to fill capillaries for microhematocrit. Each sample filled two capillaries until approximately 70% capacity, which had one of their ends sealed. Subsequently, they were centrifuged at 10,000 rpm for five minutes, and the TP concentration was determined using the plasma from one of the capillaries by refractometry. Sequentially, the second tube was subjected to 56°C (±1°C) for three minutes and re-centrifuged at 10,000 rpm for five minutes. After that, the TP concentration was measured again by refractometry. The difference between the initial

(tube one) and final (tube two) TP concentration, multiplied by 1,000, indicates the concentration of fibrinogen in the sample in mg dL^{-1}.

Tubes without EDTA, after blood collection, were left to rest for clot formation. After complete clotting, samples were centrifuged at 4,000 rpm for 10 minutes to obtain serum. From this serum, samples were taken in duplicate, which were preserved and analyzed in the Laboratory of Clinical Pathology, UNICENTRO.

At the end of the experimental period, animals were fasted from solids for 12 hours and weighed before being shipped to the slaughterhouse. Carcass gain during confinement (CGC) was evaluated, expressed in kg, according to equation 7. Based on the period of 105 days of confinement, the average carcass gain (ACG) was calculated, expressed in kg day^{-1} (equation 8). As well as the efficiency of converting the dry matter consumed into carcass (ECD), expressed in kg DM kg $carcass^{-1}$ and the efficiency of converting the weight gain into carcass ACG ADG^{-1} (%) (equation 9 and 10 respectively). For the calculations described, hot carcass weight was used.

Equation 7: CGC, kg = hot carcass weight (HCW) – Carcass weight at the beginning of the experiment, considering a theoretical hot carcass yield of 50%

$$\text{Equation 8: ACG, kg.day}^{-1} = \left(\frac{\text{CGC,kg}}{105}\right)$$

$$\text{Equation 9: ECD} = \text{ECD} = \left(\frac{\text{ADMI}}{\text{GMC, kg day}}\right)$$

Equation 10:

$$\text{ACG ADG}^{-1}(\%) = \left(\frac{\text{ACG, kg day}}{\text{ADG, kg day}}\right) * 100$$

Carcasses was measured for carcass length, arm length, arm perimeter, and thigh thickness according to the methodology suggested by Muller[16]. Carcass yield (CY) was also measured according to equation 11, as well as fat thickness, which was evaluated at four points: *longissimus dorsi*, hindquarters (sirloin cap region), ribs (ribs region) and forequarters (scapula region), using a caliper.

Equation 11:

$$\text{CY} = \left(\frac{\text{HCW}}{\text{wait at the time of shipment}}\right) * 100$$

Data regarding the performance, ingestive behavior and carcass data were tested by analysis of variance with comparison of means at 5% significance, using the SAS statistical software (1993), equation 12.

Equation 12: $Yij=\mu + Fi + Bj + Eij$

Where: Yij = dependent variables; μ = overall mean of all observations; Fi = effect of flavomycin of order "i"; Bj = effect of block of order "j" and Eij = residual random effect.

For data referring to serum parameters of the animals, the effect of the additive against the control and its effect as a function of time were evaluated, and for that they were submitted to mixed linear regression analysis (MIXED; $P<0.05$), using the SAS software (1993), equation 13.

Equation 13: $Yijk=\mu + Fi + Mj + Bk + (F*M)ij + Eijk$

Where: Yijk = dependent variables; μ = overall mean of all observations; Fi = effect of flavomycin of order "i"; Mj = effect of moment of order "j"; Bk = effect of block of order "k"; effect of the interaction between flavomycin and moment of order "ij" and Eijk = residual random effect.

Results and Discussion

From data in Table 2, the use of flavomycin promoted no changes in ADMI (kg day^{-1}), ADMI (% BW), FE and ADG of animals in relation to the control group, regardless of the evaluation periods (0 to 28; 0 to 56; 0 to 84; 0 to 105 days). Limede *et al.*[3] comparing feedlot beef cattle supplementation with different additives, including flavomycin, also observed no significant difference for ADMI and ADG between flavomycin and the control treatment. The literature points out that this additive promotes changes in the ruminal microbiota due to its mechanism of action, which can lead to improvements in animal performance[6, 7, 8], but its effect is dose and concentration dependent, which may justify the lack of significant effect in the present study, however the dose in use it is recommended by the manufacturer.

The time spent in feeding, drinking, ruminating and idleness were not altered by flavomycin supplementation, as well as the frequency of these activities (Table 3). It is suggested that these results reflect the dose of flavomycin used, that is, possibly it did not promote changes in rumen parameters, such as an increase in propionate levels, due to greater fermentation of the diet in the rumen, as reported by Edrington *et al.*[8], which would generate changes in the ingestive behavior, due to metabolic changes.

Flavomycin supplementation promoted no significant changes ($P>0.05$) on fecal output, either in natural or dry matter, as well as on fecal dry matter content and apparent digestibility of diets, with mean values of 21.48 kg day^{-1}, 3.82 kg day^{-1}, 17.56% and 61.69%, respectively (Table 3). The similarity in the production of feces, in natural and dry matter, as well as its dry matter content, may be because the diets were the same in both treatments, that is, animals were subjected to very similar conditions.

Evaluating feedlot steers fed Tifton silage and supplemented with flavomycin, Limede *et al.*[3] also observed no significant effect for the apparent digestibility of the diet in relation to the control treatment, however the mean values were lower than in the present study (53.26%), which may indicate the source of forage offered to the animals. Polizel *et al*. ([17]) and Limede *et al*. ([3]) report that the literature data regarding the impact of non-ionophores on the apparent diet digestibility and dry matter intake, when is based on forage, are inconclusive, and therefore the need for further studies and investigations to completely elucidate their action, and to prove their effect against rumen microorganisms, as reported in the literature.

Table 2. Average daily weight gain (ADG), average dry matter intake (ADMI) expressed in kg day^{-1} or per 100 kg body weight and feed efficiency (FE) of steers finished in confinement receiving flavomycin in the diet

Evaluation days	Experimental diet		Average	P value	CV (%)
	Control	Flavomycin			
Average dry matter intake (kg day-1)					
0 to 28 days	9.17	8.65	8.91	0.19	8.55
0 to 56 days	9.74	9.15	9.45	0.20	9.28
0 to 84 days	10.09	9.65	9.87	0.35	9.40
0 to 105 days	10.27	9.79	10.03	0.35	9.98
Average dry matter intake (% BW)					
0 to 28 days	2.50	2.41	2.46	0.26	5.43
0 to 56 days	2.51	2.40	2.45	0.14	5.57
0 to 84 days	2.47	2.39	2.43	0.22	4.96
0 to 105 days	2.42	2.34	2.38	0.16	4.77
Feed efficiency					
0 to 28 days	0.206	0.216	0.21	0.25	14.96
0 to 56 days	0.160	0.174	0.17	0.10	12.22
0 to 84 days	0.161	0.170	0.16	0.08	9.73
0 to 105 days	0.154	0.162	0.16	0.26	10.15
Average daily weight gain (kg day-1)					
0 to 28 days	1.897	1.857	1.88	0.81	17.83
0 to 56 days	1.573	1.594	1.58	0.85	18.35
0 to 84 days	1.633	1.641	1.64	0.95	15.89
0 to 105 days	1.595	1.592	1.59	0.97	16.61

CV: coefficient of variation.

Table 3. Ingestive behavior and fecal output of steers finished in confinement receiving flavomycin in the diet

Parameters	Experimental diet		Average	P value	CV (%)
	Control	Flavomycin			
Hours day-1					
Feed intake	3.55	3.34	3.44	0.50	17.69
Water intake	0.25	0.23	0.24	0.75	30.78
Rumination	6.82	6.77	6.79	0.93	15.07
Idleness	13.45	13.66	13.56	0.76	10.44
Times day-1					
Feed	18.44	18.31	18.38	0.93	16.69
Watering	5.31	5.30	5.31	0.99	28.03
Urination	6.75	6.93	6.84	0.83	24.13
Defecation	7.94	8.81	8.38	0.54	22.96
Fecal output, kg day-1					
Natural matter	21.78	21.19	21.48	0.70	13.81
Dry matter	3.89	3.75	3.82	0.60	13.94
Percentage %					
Dry matter of feces	17.55	17.57	17.56	0.94	3.03
Apparent digestibility	61.50	61.87	61.69	0.81	4.97

CV: coefficient of variation.

Values of carcass traits in Table 4 indicated no effect (P>0.05) of flavomycin supplementation on carcass yield, carcass weight gain, average carcass gain in kg equivalent to the period of 105 days or on the efficiency of converting the dry matter consumed into carcass, with mean values of 54.44% 1.014 kg day^{-1}, 63.48%, 106.5 kg and 10.08 kg DM kg carcass^{-1}, respectively. Likewise, there was no effect (P>0.05) of flavomycin supplementation regarding metric measures, such as carcass length, thigh thickness, arm length and perimeter, fat thickness measured in the *longissimus dorsi* muscle, in the hindquarters, ribs and forequarters.

Table 4. Carcass traits of steers finished in confinement receiving flavomycin included in the diet

Parameters	Experimental diet		Average	P value	CV (%)
	Control	Flavomycin			
Hot carcass weight (kg)	275.4	274.4	274.90	0.95	11.56
Carcass yield (%)	54.18	54.70	54.44	0.45	2.45
Average carcass gain (kg day-1)	1.004	1.025	1.014	0.84	19.84
ACG ADG-1 (%)	62.82	64.13	63.48	0.51	6.08
CGC (kg)	105.4	107.6	106.5	0.84	19.35
ECD (kg of DM kg of carcass-1)	10.41	9.74	10.08	0.18	11.82
Carcass length (cm)	132.8	131.8	132.30	0.60	3.01
Thigh thickness (cm)	20.3	20.5	20.40	0.68	4.59
Arm length (cm)	37.7	37.1	37.40	0.43	3.74
Arm perimeter (cm)	44.5	43.0	43.70	0.22	5.78
Fat thickness (mm):					
Longissimus dorsi	4.35	4.77	4.56	0.13	14.60
Hindquarters	4.56	4.94	4.75	0.20	14.81
Ribs	5.13	5.44	5.28	0.51	22.68
Forequarters	3.38	3.94	3.66	0.12	18.77

CV: coefficient of variation.

According to Lemos *et al.*[18], these measures are in line with dietary digestibility, and as mentioned above, this variable did not differ between treatments (Table 3), it is also worth noting that the additive in question has no direct effect on carcass conformation. Another factor that may justify the non-occurrence of differences between treatments for carcass parameters is the use of animals of the same genetic group, breed, age and whole, given that these are key factors for differences in these characteristics between animals[19].

When analyzing the biochemical markers that indicate liver function and inflammation (Table 5) during the experimental period, there was a significant effect of flavomycin supplementation along the evaluation period for total plasma protein, where the animals in the control group had slightly higher values than those supplemented with flavomycin, and in relation to days, there was a difference only between collection days 0 and 28. Albumin had a significant effect (P<0.05) only for the evaluation time.

Fibrinogen and GGT showed interaction between flavomycin and evaluation time. Fibrinogen had the greatest influence on the additive factor, where the animals supplemented with Flavomycin had lower values compared to the control group, and for GGT the greatest influence occurred for the evaluation time factor, where it increased while the days of evaluation have passed. According to Table 5, it was not possible to report protein deficit coming from the diet, given that the values of total protein and albumin are within the reference values for the species, and it cannot also infer that they carried diseases hepatic level because the values of albumin, which is the main plasma protein synthesized in the liver, and AST, which indicates hepatic function, are also within the reference levels for the species (Table 5).

Variations in serum parameters during the confinement period are related to age. In a study evaluating these same serum parameters and with animals of the same age, changes were also observed during the confinement period, however the literature reports that the levels of TP, albumin, fibrinogen, AST, GGT are directly influenced by the animal age, because until puberty, there are changes in their metabolism and body composition, such as changes in the rate of bone, muscle and fat tissue deposition[21, 22].

Values of fibrinogen, the main marker of an acute inflammatory process, were initially low and presented

an increase in control animals, while the opposite occurred for animals supplemented with flavomycin. These results may be justified by the inhibitory effect of this additive on the production of *Fusobacterium* spp, which is the main responsible for causing liver damage in ruminants, demonstrating its effectiveness in suppressing these microorganisms[23].

Table 5. Biochemical markers related to liver function and inflammation on different evaluation days

Evaluation	Experimental diet		P value			
	Control	Flavomycin	** P	*** F	*** T	*** F*T
Total plasma protein (TP; g dL-1)						
Day 0	7.24 ± 0.26	6.93 ± 0.43	0.08	0.01	0.04	0.18
Day 28	7.40 ± 0.44	7.01 ± 0.20	0.03			
Day 56	7.16 ± 0.40	7.07 ± 0.14	0.54			
Day 84	7.07 ± 0.32	6.89 ± 0.25	0.20			
Reference value	7.0 – 8.9*					
Albumin (mg dL-1)						
Day 0	2.25 ± 0.21	2.21 ± 0.21	0.67	0.85	<0.001	0.66
Day 28	2.68 ± 0.20	2.76 ± 0.25	0.46			
Day 56	2.82 ± 0.35	3.01 ± 0.24	0.21			
Day 84	2.84 ± 0.16	2.85 ± 0.25	0.96			
Reference value	2.6 – 3.6*					
Fibrinogen (g dL-1)						
Day 0	288.89 ± 105.41	422.22 ± 210.82	0.13	0.02	0.22	<0.001
Day 28	296.44 ± 83.63	293.44 ± 50.66	0.93			
Day 56	358.22 ± 99.85	286.78 ± 67.61	0.09			
Day 84	326.33 ± 64.47	256.56 ± 57.44	0.03			
Reference value	300 – 700*					
Aspartate aminotransferase (AST; IU L-1)						
Day 0	64.67 ± 20.51	62.22 ± 15.79	0.95	0.34	0.28	0.76
Day 28	89.56 ± 17.35	74.22 ± 10.49	0.04			
Day 56	66.44 ± 13.39	63.00 ± 7.75	0.51			
Day 84	80.00 ± 12.67	70.56 ± 10.71	0.11			
Reference value	48.0 – 89.5*					
Gamma-glutamyltransferase (GGT; IU L-1)						
Day 0	23.00 ± 4.58	25.67 ± 11.54	0.92	0.62	<0.001	0.02
Day 28	27.33 ± 5.66	23.89 ± 6.49	0.25			
Day 56	27.33 ± 5.66	24.78 ± 5.43	0.34			
Day 84	33.33 ± 10.28	26.44 ± 7.06	0.10			
Reference value	9.2 – 24.3*					

IU: international unity;
*Source of reference values: Kaneko[20]
**P-value related to the *t*-test (P<0.05).
***Prob values > F related to Mixed Linear Regression Analysis (MIXED; P<0.05).

As for biochemical markers of renal function (urea and creatinine) when evaluated during the experimental period (Table 6), only urea had a significant effect on the time factor, but values are within the reference range for the species. Comparing these parameters between control animals and those supplemented with flavomycin, a difference (P<0.05) was detected for urea at 28 days and creatinine at 84 days, in which urea levels were lower for the supplemented group (28.00 mg dL^{-1}) and higher creatinine was found for the supplemented group compared to the control group (1.80 mg dL^{-1}), but within the reference range for the species.

Table 6. Serum biochemical markers of renal function on different evaluation days

Evaluation	Experimental diet		P value			
	Control	Flavomycin	** P	*** F	*** T	*** F*T
Urea (mg dL-1)						
Day 0	22.33 ± 3.08	22.56 ± 2.83	0.88	0.67	<0.001	0.96
Day 28	30.44 ± 3.24	28.00 ± 2.00	0.07			
Day 56	35.89 ± 5.44	34.11 ± 7.34	0.57			
Day 84	31.67 ± 7.21	31.44 ± 4.45	0.94			
Reference value	28.7 – 48.8*					
Creatinine (mg dL-1)						
Day 0	1.54 ± 0.23	1.50 ± 0.24	0.70	0.77	0.85	0.33
Day 28	1.16 ± 0.39	1.26 ± 0.33	0.57			
Day 56	1.19 ± 0.27	1.17 ± 0.28	0.87			
Day 84	1.57 ± 0.22	1.80 ± 0.23	0.04			
Reference value	1.1 – 1.9*					

*Source of reference values: Kaneko[20]

**P-value related to the *t*-test (P<0.05).

***Prob values > F related to Mixed Linear Regression Analysis (MIXED; P<0.05).

Even with these differences, it is suggested that there was no occurrence of renal dysfunction in the animals, as the serum levels of these markers are within the reference range for the species. Creatinine, for example, is a marker extremely influenced by the breed of the animal, a factor that must be taken into account for the correct interpretation of laboratory tests[24].

Conclusion

Flavomycin did not improve performance, nor did it change the ingestive behavior and carcass traits of the animals. Values of TP at 28 days, fibrinogen at 84 days, AST at 84 days and creatinine at 84 days were lower for animals supplemented with flavomycin. In relation to the experimental period, there was a reduction in serum levels of TP, an increase in albumin, GGT and urea, but all remained within the reference range for the species.

Conflict of interests

The authors declare no conflict of interest

Author contributions

Conceptualization: M. Neumann*; Data curation:* A. M. Souza; *Formal analysis:* M. Neumann*; Investigation:* A. M. Souza, M. K. Falbo, H. G. Bertagnon, L. Costa and F. S. Sidor*; Methodology:* M. Neumann and M. K. Falbo*; Project Management:* A. M. Souza*; Resources:* M. Neumann, M. K. Falbo and H. G. Bertagnon*; Supervision:* M. Neumann; Writing: A. M. Souza and M. Neumann.

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