SEMINA
Ciências Agrárias

DOI: 10.5433/1679-0359.2023v44n1p343

Comparative evaluation of the efficacy of different marbofloxacin-based products in pigs at the nursery, growth and finish phases with clinical signs of respiratory disease

Avaliação comparativa da eficácia de diferentes produtos à base de marbofloxacina em suínos nas fases de creche, crescimento e terminação com sinais clínicos de doenças respiratórias

Caio Abercio da Silva[1]*; André Maurício Buzato[2]; Gabriela Souza Romano[3]; Cleandro Pazinato Dias[3]; Kelly Lais Souza[3]; Marco Aurélio Callegari[3]; Rafael Humberto Carvalho[1]

Highlights

Marbofloxacin is highly effective in the treatment of swine respiratory diseases.
The article addresses the quality of commercial marbofloxacins.
The SISAAB is an effective procedure for the treatment of swine respiratory diseases.

Abstract

Marbofloxacin is one of the antibiotics of choice for the treatment of pigs with clinical manifestations of respiratory disease. Some commercial products on the market contain this active ingredient, and the objective of this study was to evaluate the efficacy of 3 available marbofloxacin-based products based on the SISAAB (single injection and short-term antibiotic) concept with regard to the performance and health parameters of pigs in the nursery, growth and finish phases with clinical manifestations of respiratory disease (RD). A total of 78 animals with clinical manifestations of RD from a total of 1726 pigs were used. The animals that had RD symptoms were weighed, identified and randomly subjected to 3 treatments: T1 - Forcyl® (n = 27); T2 - Marbox® (n = 25); T3 - Resolutor® (n = 26). All treatments corresponded to a single intramuscular dose of 8 mg of marbofloxacin per kg of live weight. After treatment, clinical signs of cough and depression, water consumption, rectal temperature, performance parameters, lung lesions and the

[1] Profs. Drs., Universidade Estadual de Londrina, UEL, Londrina, PR, Brazil. E-mail: casilva@uel.br; rafael.carvalho@uel.br
[2] Researcher, Vetoquinol Saúde Animal Ltda., Vetoquinol, Aparecida de Goiânia, GO, Brazil. E-mail: andre.buzato@vetoquinol.com
[3] Researchers, Akei Animal Research, AKEI, Fartura, SP, Brazil. E-mail: gabrieli.romano@akei.agr.br; cleandro@cleandrodias.com.br; tecnico@akei.agr.br; contato@akei.agr.br
* Author for correspondence

Received: Set. 28, 2022 Approved: Mar. 09, 2023

pneumonia index of the animals were evaluated. The animals that received T1 and T3 maintained a mean rectal temperature of 39.38 °C 2 days after administration. In contrast, animals in the group that received T2 had significantly higher temperatures (p = 0.068) in this period (39.53 °C). There was a greater decrease in temperature (p = 0.042) in the 24 hours after drug administration in animals that received T1 (-0.573 °C). Regarding the other performance parameters, clinical signs of cough and depression, water consumption, lung injury and the pneumonia index, no differences were observed between the marbofloxacin-based products evaluated (p > 0.05). All marbofloxacin-based products were effective in reducing the clinical signs of RD and promoting animal performance and health. However, T1 was more effective in reducing the rectal temperature of the animals.
Key words: Antibiotics. Performance. Pneumonia. Cough.

Resumo

A marbofloxacina é um dos antibióticos selecionados para o tratamento de suínos com manifestações clínicas de doenças respiratórias. Existem alguns produtos comerciais no mercado com este princípio ativo, nesse sentido, objetivou-se com esse trabalho avaliar, com base no conceito SISAAB (antibioticoterapia de curta duração e dose única), a eficiência de três marbofloxacinas disponíveis sobre os parâmetros de desempenho e saúde de suínos em fase de creche, crescimento e terminação com quadros clínicos de doenças respiratórias (DR). Foram utilizados 78 animais com manifestações clínicas de DR de um total de 1726 porcos. Os animais que apresentaram sintomas de DR foram pesados, identificados e submetidos aleatoriamente a 3 tratamentos: T1 - Forcyl® (n = 27); T2 - Marbox® (n = 25); T3 - Resolutor® (n = 26). Todos os tratamentos corresponderam a uma dose única intramuscular de 8 mg de marbofloxacina por kg de peso vivo. Após o tratamento, foram avaliados os sinais clínicos de tosse e depressão, consumo de água, temperatura retal, parâmetros de desempenho, lesões pulmonares e o índice de pneumonia dos animais. Os animais que receberam T1 e T3 mantiveram temperatura retal média de 39,38°C, 2 dias após a administração. Em contrapartida, os animais do grupo que recebeu T2 apresentaram temperaturas significativamente mais elevadas (p < 0,10) neste período (39,53 °C). Em linha, foi possível observar a maior diminuição de temperatura (p = 0,042) nas 24 horas após a aplicação da medicação nos animais do grupo T1 (-0,573 °C). Em relação aos demais parâmetros de desempenho, sinais clínicos de tosse e estado de depressão, consumo de água, lesões pulmonares e índice de pneumonia, não foram observadas diferenças entre as marboloxacinas avaliadas (p>0,05). Todas as marbofloxacinas foram eficazes na redução dos sinais clínicos de doenças respiratórias, promovendo o desempenho e saúde dos animais, entretanto foi constatada a maior eficiência de T1 na redução da temperatura retal dos animais.
Palavras-chave: Antibióticos. Desempenho. Pneumonia. Tosse.

Introduction

Marbofloxacin is a third-generation synthetic fluoroquinolone developed exclusively for veterinary use, administered orally or parenterally in several species, including pigs. For this species, marbofloxacin is used for the treatment of respiratory diseases caused by *Pasteurella multocida, Actinobacillus pleuropneumoniae, Streptococcus* suis and *Glaesserella parasuis,* with a recommended dose of 2 mg per kilogram of live weight every 24 hours for 5 or more days (Dorey et al., 2017; European Medicines Evaluation Agency [EMEA], 1998; Lees & Shojaee Aliabadi, 2002; Schneider et al., 2014).

These pathogenic respiratory agents are endemic and responsible for recurrent clinical conditions, commonly referred to as the swine respiratory disease complex (SRDC), which is considered one of the main causes of morbidity and mortality in pig farming (Opriessnig et al., 2011), often resulting in substantial economic losses (Biberstein, 1990; Hossain et al., 2017; Nedbalcova et al., 2006). In addition, when these diseases intensify, they cause a decrease in the growth rate during fattening and increase production costs due to the required use of antimicrobials for treatment, with negative economic consequences.

Marbofloxacin is an antibiotic of choice for respiratory problems due to its high efficacy, rapid absorption, good distribution, broad spectrum and low level of bacterial resistance (Nedbalcova et al., 2019). As a lipid-soluble organic acid with low/moderate binding to plasma proteins, it achieves good tissue penetration and wide distribution (Lees & Shojaee Aliabadi, 2002), with higher concentrations in lung tissue, exceeding the concentrations found in plasma (Dorey et al., 2017; Lees & Shojaee Aliabadi, 2002).

Thus, marbofloxacin is one of the most commonly used active ingredients for the treatment of RD in pigs. In a meta-analysis by O'Connor et al. (2019) in which 34 relevant studies on injectable antibiotic options for the treatment of naturally occurring porcine respiratory diseases were included, marbofloxacin was identified as one of the most important active ingredients used and was associated with a lower risk of failure in treatment outcomes.

Because of these characteristics, there are several commercial products based on marbofloxacin available on the market (Sargeant, 2018). However, although these products have the same active ingredients, their bioequivalence may not be similar because they have different maximum plasma concentrations (Cmax) and mean times to reach the Cmax.

Comparative studies of marbofloxacin with other antibiotics for the same purposes have been conducted, highlighting the study by Thomas et al. (2000), who evaluated marbofloxacin and amoxicillin; the study by Nedbalcova et al. (2019), who compared marbofloxacin, amoxicillin and enrofloxacin; and the meta-analysis conducted by O'Connor et al. (2019), in which several antibiotics were included. However, comparisons of the same active ingredient, marbofloxacin, with commercial drugs from different sources are scarce.

Considering the benefits of marbofloxacin in the treatment of respiratory pathogens and the possible differences in the effectiveness of different commercial preparations of marbofloxacin with regard to a reduction in the clinical signs of these diseases, the aim of this study was to evaluate the efficacy of 3 marbofloxacin commercial preparations with regard to the performance parameters and health of pigs in the nursery phase, growth and finish stages with clinical manifestations of respiratory disease.

Material and Methods

The procedures adopted in this study were performed in accordance with the practices approved by the Ethics Committee on the Use of Research Animals of Akei Animal Research (protocol number 019/20) and international animal welfare guidelines.

Animals, housing and feed

A total of 1,726 castrated males and females (PIC® genetics, Camborough x AG 337) on a commercial farm were evaluated in 4 experimental units (2 weaned-to-finish units and 2 growth and termination units). In both units, the pen area per animal was 1.0 m^2.

A total of 1046 animals were monitored during the weaned-to-finish phases, i.e., between 21 and 165 days of age, and 680 animals were monitored in the growth and finish phases, i.e., between 63 and 165 days of age. The pigs were housed in groups of 3 to 6 animals per pen, respecting the minimum housing area required per animal.

All animals received diets free of growth promoters and were subjected to preventive shocks with antibiotics via water or feed. The nutritional programme adopted was based on the use of 8 feeds, i.e., 4 for the weaned-to-finish phase (preinitial I and II and initial I and II) and 4 for the growth and finish phases (growth I and II and finish I and II). Throughout the study period, the animals received water and feed *ad libitum.*

Animal selection and treatment

Seventy-eight pigs from a total of 1,726 presented clinical respiratory problems based on signs of coughing, sneezing, increased respiratory rate, and prostration, among others, with reference to Christensen et al. (2006).

The animals were randomized, considering sex, to receive 1 of 3 experimental treatments with commercial preparations of marbofloxacin: T1 - Forcyl®, 16% (Vetoquinol SA, Lure, France); T2 - Marbox®, 10% (Ceva Animal Health, Turkey); and T3 - Resolutor®, 20% (Ouro Fino Saúde Animal Ltda., Cravinhos, Brazil).

After randomization, age and clinical signs were recorded. The pigs were weighed, identified and received 8 mg of marbofloxacin per kg of live weight as a single intramuscular dose. There were 27, 25 and 26 animals in the T1, T2 and T3 groups, respectively.

During the 10 days after administration, the presence or absence of water consumption was evaluated daily, as were clinical signs of depression and cough. The assessment of depression followed the methodology described by Rossi et al. (2021).

Respiratory rate (normal or abnormal) and rectal temperature were evaluated on the first and second days after drug application. Live weight and average daily weight gain were measured on the first, fifth and tenth days after drug administration.

At 165 days of age, pigs in the weaned-to-finish group and growth and termination group were sent to a commercial slaughterhouse. After slaughter, signs of lung injury were evaluated, and the pneumonia index was calculated. In total, 48 animals were analyzed (17, 15 and 16 animals in the T1, T2 and T3 groups, respectively).

Statistical analysis

The distribution of the data was analyzed using the Kolmogorov-Smirnov & Lilliefors and Shapiro-Wilk's W tests ($p > 0.05$). Data with a normal distribution were subjected to analysis of variance, and means were subjected to Tukey's test. Nonnormally distributed and qualitative and quantitative data were compared using the Kruskal-Wallis test using Statistics for Windows®, version 10.0. For both tests, a "p" value less than 0.05 was considered significant, and a "p" value between 0.05 and 0.10 was considered a trend.

Results and Discussion

The animals that received T1 and T3 maintained a mean rectal temperature of 39.38 °C 2 days (D2) after drug administration (Table 1). In contrast, piglets that received T2 had higher temperatures ($p = 0.068$) in this period. Additionally, the greatest decrease in temperature ($p = 0.042$) in the 24 hours after administration occurred in animals that received T1, with differences of 0.093 and 0.296 °C from animals that received T2 and T3, respectively.

Table 1
Mean rectal temperature of pigs treated with different marbofloxacin-based drugs

Parameter	Marbofloxacin			CV (%)	p value
	T1	T2	T3		
Temperature D1 (°C)	39.950	40.012	39.662	1.68	0.1346
Temperature D2 (°C)	39.377b	39.532a	39.385b	1.31	0.0680
Difference D2 - D1 (°C)	-0.573a	-0.480ab	-0.277b	157.11	0.0424

[a - c] Different letters in rows indicate differences by the Kruskal-Wallis test ($p < 0.05$) and trends ($0.05 < p < 0.10$). D1: Day 1; D2: Day 2.

In the evaluation of the performance of the animals, post administration, there was no difference ($p > 0.05$) in mean body weight and mean daily weight gain on days 1 (D1), 5 (D5) and 10 (D10) among the groups of treated animals (T1, T2 and T3) (Table 2).

Table 2
Mean live weight (LW) and daily weight gain (DWG) on Days 1 (D1), 5 (D5) and 10 (D10) after the administration of different marbofloxacin-based products in pigs

Parameter	Marbofloxacin			CV (%)	p value
	T1	T2	T3		
PV D1 (kg)	71.987	68.238	70.256	34.69	0.9158
PV D5 (kg)	76.658	72.712	74.685	32.87	0.9047
PV D10 (kg)	81.588	77.656	79.173	31.64	0.9136
GPD D1-D5 (kg)	4.671	4.474	4.429	44.52	0.8395
GPD D5-D10 (kg)	4.931	4.944	4.488	39.41	0.6440
GPD D1-D10 (kg)	9.602	9.418	8.917	31.87	0.6791

[a - c] Different letters in rows indicate differences by the Tukey test or Kruskal-Wallis test ($p < 0.05$) and trends ($0.05 < p < 0.10$). D1: Day 1; D5: Day 5 and D10: Day 10.

Regarding water consumption and depression from day 1 to day 10 (D10) after drug administration, no differences were observed among the marbofloxacin-based products used ($p > 0.05$).

Regarding clinical signs of cough (Table 3), 10 days after drug administration, no differences were found among the preparations used ($p > 0.05$). However, as a trend ($p = 0.0714$), compared to animals that received T3 ($n = 24$), fewer animals that received T1 ($n = 18$) and T2 ($n = 20$) exhibited coughing 10 days after drug administration. Regarding the parameters of water consumption and depression status (Table 4) from day 1 to day 10 (D10) after the use of the drugs, no differences were detected between the marbobloxacins used ($p>0.05$).

Tables 5 and 6 show, based on the marbofloxacin preparation administered, the number and percentage of animals with pneumonia lesions in different lung regions and the mean degree of involvement of the lesions in the lung regions, respectively, in addition to the pneumonia index. There was no difference among treatments regarding the degree of lesion involvement in the lung regions. For the pneumonia index, the value was lower ($p = 0.1214$) for T1 than for T2 and T3, but the difference was not significant.

Table 3
Number and percentage of animals that exhibited coughing from Day 1 (D1) to Day 10 (D10) after drug administration

Parameter	Marbofloxacin			p value
	T1 (n = 27)	T2 (n = 25)	T3 (n = 26)	
Cough D1 (n)	18b	20ab	24a	0.0714
Cough D2 (n)	18	16	20	0.5734
Cough D3 (n)	10	10	12	0.7926
Cough D4 (n)	3	6	8	0.2157
Cough D5 (n)	4	5	5	0.8707
Cough D1 - D5 (n)	14	15	19	0.2829
Cough D6 (n)	4	4	4	0.9931
Cough D7 (n)	3	0	2	0.2538
Cough D8 (n)	3	0	4	0.1442
Cough D9 (n)	1	1	2	0.7701
Cough D10 (n)	0	0	0	1.0000
Cough D1 (%)	66.67	80.00	92.31	- -
Cough D2 (%)	66.67	64.00	76.92	- -
Cough D3 (%)	37.07	40.00	46.15	- -
Cough D4 (%)	11.11	24.00	30.77	- -
Cough D5 (%)	14.81	20.00	19.23	- -
Cough D6 (%)	14.81	16.00	15.38	- -
Cough D7 (%)	11.11	0.00	7.69	- -
Cough D8 (%)	11.11	0.00	15.38	- -
Cough D9 (%)	3.70	4.00	7.69	- -
Cough D10 (%)	0.00	0.00	0.00	

[a-c] different letters in rows indicate trends by the Kruskal-Wallis test ($p < 0.05$) and trends ($0.05 < p < 0.10$).

Table 4
Number of pigs that did not consume water (DCW) and exhibited signs of depression from Day 1 (D1) to Day 10 (D10) after drug administration

Parameter	Marbofloxacin			p value
	T1 (n = 27)	T2 (n = 25)	T3 (n = 26)	
DCW D1 (n)	2	1	0	0.3739
DCW D2 (n)	0	1	0	0.3465
DCW D3 (n)	0	1	0	0.3465
DCW D4 (n)	0	1	0	0.3465
DCW D5 (n)	0	0	0	1.0000
DCW D6 (n)	0	0	0	1.0000
DCW D7 (n)	0	1	0	0.3465
DCW D8 (n)	0	1	0	0.3465
DCW D9 (n)	0	0	0	1.0000
DCW D10 (n)	0	0	0	1.0000
Depression D1 (n)	4	3	0	0.1409
Depression D2 (n)	0	1	0	0.3465
Depression D3 (n)	0	1	0	0.3465
Depression D4 (n)	0	1	0	0.3465
Depression D5 (n)	0	0	0	1.0000
Depression D6 (n)	0	1	0	0.3465
Depression D7 (n)	0	1	0	0.3465
Depression D8 (n)	0	1	0	0.3465
Depression D9 (n)	0	0	0	1.0000
Depression D10 (n)	0	0	0	1.0000

[a - c] different letters in rows indicate trends by the Kruskal-Wallis test ($p < 0.05$) and trends ($0.05 < p < 0.10$).

Comparative scientific studies that evaluate marbofloxacin as an active ingredient of different commercial products for parenteral use, aiming to identify those preparations that have better efficacy with regard to alleviating clinical signs of respiratory diseases in pigs, are nonexistent; in contrast, there are *in vivo* and *in vitro* studies that evaluated the effects of different doses of marbofloxacin (milligrams of active ingredient per kilogram of live weight) (Vilalta et al., 2011, 2014) and compared marbofloxacin to other antibiotics and different therapeutic regimens (single dose versus 2 or more doses) (Dorey et al., 2017; Hoeltig et al., 2018; Nedbalcova et al., 2019). In this sense, this study, which compared 3 marbofloxacin-based commercial products, is unprecedented.

Table 5
Number and percentage of animals with lesions in different regions of the lung based on the marbofloxacin preparation administered

Parameter	Marbofloxacin					
	T1 (n = 17)		T2 (n = 15)		T3 (n = 16)	
	n	%	n	%	n	%
Right apical (n)	5	29.41	5	33.33	4	25.00
Right heart	7	41.18	7	46.67	6	37.50
Right diaphragm	1	5.88	1	6,67	4	25.00
Left apical	1	5.88	2	13.33	2	12.50
Left heart	5	29.41	2	13.33	5	31.25
Left diaphragm	3	17.65	4	26.67	2	12.50
Intermediate	3	17.65	3	20.00	3	18.75

Table 6
Mean degree of lesion involvement in lung regions and the pneumonia index in pigs based on the marbofloxacin preparation administered

Parameter	Marbofloxacin					
	T1 (n = 17)		T2 (n = 15)		T3 (n = 16)	
	n	%	n	%	n	%
Right apical	0.706	0.933	0.688	0.2497	4	25.00
Right heart	1.000	1.067	1.063	0.8077	6	37.50
Right diaphragm	0.647	0.467	0.563	0.6437	4	25.00
Left apical	0.706	0.667	0.625	0.9521	2	12.50
Left heart	0.647	0.667	1.000	0.7156	5	31.25
Left diaphragm	0.471	0.933	0.750	0.2490	2	12.50
Intermediate	0.765	0.867	0.500	0.6091	3	18.75
Pneumonia index	1.353	1.800	1.563	0.1214		

Regarding body temperature, post administration, T1 resulted in a significant reduction ($p < 0.042$) in temperature 24 hours after administration (-0.573 *versus* -0.480 and -0.277 °C for T1, T2 and T3, respectively). This result indicates that T1 may have pharmacokinetics different from those of T2 and T3. In line with this observation, Ding et al. (2010) and Schneider et al. (2014) found that the absolute bioavailability of marbofloxacin in weaned and fattening pigs varies between 90 and 100%, regardless of the dose or concentration of the product. This range of bioavailability, cited by the authors, may

represent the reason for the differences for this parameter in favor of T1 and support the hypothesis of our study that there are differences in different marbofloxacin-based products in the treatment of respiratory problems in pigs.

In this study, the results regarding rectal temperature were similar to those obtained by Zou and Zeng (2012), who reported the success of marbofloxacin on the basis of improvements in the rectal temperature of pigs experimentally infected with *Actinobacillus pleuropneumoniae;* 24 hours after the administration of marbofloxacin, regardless of the dose, the rectal temperature of the animals was similar to that of the animals in the negative control group (no challenge) and significantly lower than those in the infected and untreated group.

Considering that for all treatments, the animals received the same dosage of marbofloxacin (8 mg/kg live weight, single dose), the differences in rectal temperature may be due to the pharmacokinetic characteristics of the products evaluated. Hossain et al. (2017), when studying the pharmacokinetics of the same marbofloxacin-based product used as the T1 treatment in this study, reported a Cmax of 2.59 µg/mL and a Tmax of 0.44 h at a dose of 2.5 mg/kg live weight for growing pigs, differing from the results for other commercial marbofloxacin-based products in studies by Ding et al. (2010) and Yang et al. (2017), who also worked with a dose of 2.5 mg/kg live weight and observed Cmax and Tmax values of 1.62 µg/mL and 2.00 h and 1.83 µg/mL and 0.71 h, respectively.

The T1 Cmax values obtained by Hossain et al. (2017) were 59.87% and 41.53% higher than those for marbofloxacin evaluated by Ding et al. (2010) and Yang et al. (2017), respectively. For Tmax, the values were also better for T1, similar to that reported by Hossain et al. (2017), being 4.54 and 1.61 times shorter to reach the maximum concentration of the active drug than those observed for the marbofloxacin-based products studied by Ding et al. (2010) and Yang et al. (2017), respectively. Based on these results, it is pertinent to consider in our study that the advantages of T1 in relation to T2 and T3 with regard to rectal temperature may be due to distinct proprietary pharmacokinetic conditions for each commercial.

As a consequence of the febrile state, animals may exhibit some behavioral effects, such as depression (Escobar et al., 2007). In this study, there were no differences among treatments regarding the presence of depression in animals in the 10 days following drug administration. Depressive states in sick animals are particularly evident at the beginning of the disease process before tissue damage is caused by the pathogen (Hart, 2009). This fact may explain the presence of depression only on D01 in animals that received T1.

Regarding the effect of treatments on zootechnical performance, as evaluated by the number of animals that did not show interruption of water consumption after treatment, measured over 10 days after drug administration (Table 4), and by the live weight and weight gain at 3 time points after drug administration (1, 5 and 10 days), the results indicate that there were no advantages for any of the treatments. This condition, however, confirms the effective action of marbofloxacin, which despite being

of different commercial origins, presumably ensured that the animals, even under a clinical respiratory condition, would, in the first days after drug administration, consume water and consequently continue to consume water and food and thus gain weight (Table 2). Additionally, there were no differences among treatments regarding the presence of depression in animals in the 10 days following drug administration.

The observed weight gain, which was not different ($p < 0.05$) among treatments in our study, is similar to the results obtained by Zou and Zeng (2012), who, although employing a programme different from the one in our study, i.e., the administration of 3 different doses of marbofloxacin (1.5, 2.5 and 5.0 mg/kg, intramuscularly, for 4 consecutive days) to pigs with an average weight of 16 kg experimentally infected with *Actinobacillus pleuropneumoniae,* observed significant weight gains after 4 weeks but proportionally higher weight gains based on the dose administered. These results reinforce that the benefits of marbofloxacin, regardless of the commercial product evaluated, have an interface with consumption, weight gain and homeothermy.

In the evaluation of the reduction in the clinical signs of cough (Table 3), which could represent an effect associated with product pharmacokinetics, translated by a greater and faster presence of the active drug in the lungs, no advantages for any of the treatments were observed. All treatments were equally efficient in eliminating these signs of cough up to 10 days after drug administration. This finding reinforces that marbofloxacin should be an antibiotic of choice for this class of diseases, regardless of the source used; our results are similar to those reported by Hoeltig et al. (2018), who also used 8 mg/kg of marbofloxacin per kilo of live weight in a single dose and compared the results (reduction in cough) with those for enrofloxacin (2.5 mg/kg of live weight for 3 consecutive days) and a negative control group, with marbofloxacin being better than enrofloxacin for the treatment of respiratory diseases.

The mode of use of marbofloxacin adopted for all treatments in our study is based on a new concept for the use of injectable antibiotics, i.e., SISAAB (short-term antibiotic and single injection), which proposes the use of a high dosage of bactericidal antibiotic, seeking the resolution of a health problem under a minimum period of antibiotic exposure, which favors natural immunity after resolution of infection/inflammation. This therapeutic concept is supported by the mutation prevention concentration (MPC), defined as the minimum inhibitory concentration (MIC) of the least sensitive mutant strain. Briefly, the procedure involves the use of an antibiotic dose 4 to 8 times higher than the MIC 90 dose for the bacterial population of the mutant strain (Grandemange et al., 2017). In this study, the dose used (8 mg/kg live weight, under a single dose) is consistent with the SISAAB concept because it is 4 times the classically recommended dose of marbofloxacin for intramuscular use in pigs, i.e., 2 mg/kg body weight (EMEA, 1998).

The localized inflammatory response to respiratory diseases may contribute to the development of perceptible macroscopic lung lesions (Garcia-Morante et al., 2016). In this study, the evaluation of lung lesions

and the calculation of the pneumonia index (Tables 5 and 6) revealed similar results among all products regarding the degree of involvement of lung lesions; however, for the pneumonia index, a lower value for T1 (1.353) than for T2 and T3 (1.800 and 1.563, respectively) suggests an advantage (P = 0.121) for the previous one. This finding could again be related to the possible pharmacokinetic differences between the tested products. However, notably, regardless of these differences, the results obtained were similar to those reported by Hoeltig et al. (2018), i.e., marbofloxacin reduced lung lesions. Additionally, the authors found that marbofloxacin showed better results than enrofloxacin, recommending it as an antibiotic of choice for respiratory problems (Hoeltig et al., 2018).

In this regard, our results can also be compared to those obtained by Nedbalcova et al. (2019), who conducted an in vitro study to determine the best postantibiotic effects (PAEs) against the agents *A. pleuropneumoniae, Glaesserella. parasuis* and *P. multocida,* an evaluation concept that is defined as the period of suppression of bacterial growth that persists after the limited exposure of organisms to antimicrobials (Craig & Gudmundsson, 1996). The authors observed that the PAE of marbofloxacin was longer than those for all evaluated agents; notably, the PAE for enrofloxacin was similar to that for marbofloxacin for *A. pleuropneumoniae* and *H. parasuis* but shorter than that for marbofloxacin for *P. multocida.* Conversely, compared to the other 2 antibiotics, amoxicillin showed lower PAEs for all 3 pathogens.

These findings confirm that marbofloxacin exhibits excellent pharmacokinetics after parenteral administration, with high tissue concentrations, low plasma protein binding, a long and effective half-life and wide tissue distribution (Haritova et al., 2006; Sun et al., 2015).

Additionally, a study to monitor susceptibility to marbofloxacin in respiratory tract infections in Europe from 2005 to 2013 (El Garch et al., 2017) identified that marbofloxacin susceptibility was very high as a whole, with 0.4% of microbial selection observed for *Streptococcus suis* (729 isolates), a cause of respiratory disease. Other respiratory pathogens were also highly susceptible to marbofloxacin, without presenting selection for *Actinobacillus pleuropneumoniae* in 647 isolates evaluated and for Bordetella bronchiseptica in 504 isolates evaluated, with only 0.1% selection for *Pasteurella multocida* (1373 isolates) and 1.4% selection for *Glaesserella parasuis* (145 isolates).

In support of the results obtained herein, the benefits of programmes that adopt the use of higher doses of marbofloxacin for the control of pathogens were corroborated by Zou and Zeng (2012), who reported that the cure rate for pigs infected with *Actinobacillus pleuropneumoniae* was greater than 90% for the dose of 5 mg/kg live weight *versus* 80 and 60% for doses of 2.5 and 1.5 mg kg live weight, respectively. In addition to the benefit of using a single high concentration dose, this strategy reduces the amplification of bacterial selection (Vallé et al., 2012), as also observed by Vilalta et al. (2011) when evaluating the effect of 8 mg of marbofloxacin per kg of live weight compared to those of 2 and 4 mg of marbofloxacin per kg of live weight.

Conclusion

The three marbofloxacin evaluated generates effective responses in animals affected by respiratory diseases, highlighting Forcyl® for presenting a more intense reduction in rectal temperature compared to the other marbofloxacin-based products evaluated.

References

Biberstein, E. L. (1990). Our understanding of the Pasteurellaceae. *Canadian Journal of Veterinary Research = Revue Canadienne de Recherche Veterinaire, 54*(Suppl.), S78-82.

Christensen, G., Sorensen, V., & Mousing, J. (2006). Diseases of the respiratory system. In J. J. Zimmerman, L. A. Karriker, K. J. Schwartz, G. W. Stevenson, & A. Ramirez (Eds.), *Diseases of swine* (9nd ed., pp. 913-940). Ames.

Craig, W. A., & Gudmundsson, S. (1996). The postantibiotic effect. In V. Lorian (Ed.), *Antibiotics in laboratory medicine* (4nd ed., pp. 296-329). Baltimore The Williams & Wilkins Co.

Ding, H., Li, Y., Chen, Z., Rizwan-Ul-Haq, M., & Zeng, Z. (2010). Plasma and tissue cage fluid pharmacokinetics of marbofloxacin after intravenous, intramuscular, and oral single-dose application in pigs. *Journal of Veterinary Pharmacology and Therapeutics, 33*(5), 507-510. doi: 10.1111/j.1365-2885. 2010.01164.x

Dorey, L., Pelligand, L., & Lees, P. (2017). Prediction of marbofloxacin dosage for the pig pneumonia pathogens Actinobacillus pleuropneumoniae and Pasteurella multocida by pharmacokinetic/pharmacodynamic modelling. *BMC Veterinary Research, 13*(1), 1-10. doi: 10.1186/s12917-017-1128-y

El Garch, F., Kroemer, S., Galland, D., Morrissey, I., & Woehrle, F. (2017). Survey of susceptibility to marbofloxacin in bacteria isolated from diseased pigs in Europe. *Veterinary Record, 180*(24), 34-60. doi: 10.1136/vr.103954

European Medicines Evaluation Agency - EMEA (1998). *Committee for veterinary medicinal products - Mecillinam.* Report.

Escobar, J., van Alstine, W. G., Baker, D. H., & Johnson, R. W. (2007). Behaviour of pigs with viral and bacterial pneumonia. *Applied Animal Behaviour Science, 105*(1-3), 42-50. doi: 10.1016/j.applanim.2006.06.005

Garcia-Morante, B., Segalés, J., Fraile, L., Pérez de Rozas, A., Maiti, H., Coll, T., & Sibila, M. (2016). Assessment of Mycoplasma hyopneumoniae-induced pneumonia using different lung lesion scoring systems: a comparative review. *Journal of Comparative Pathology, 154*(2-3), 125-134. doi: 10.1016/J.JCPA.2015.11.003

Grandemange, E., Perrin, P. A., Cvejic, D., Haas, M., Rowan, T., & Hellmann, K. (2017). Randomised controlled field study to evaluate the efficacy and clinical safety of a single 8 mg/kg injectable dose of marbofloxacin compared with one or two doses of 7.5 mg/kg injectable enrofloxacin for the treatment of Actinobacillus pleuropneumoniae infections in growingfattening pigs in Europe. *Porcine Health Management, 3*(1), 1-12. doi: 10.1186/S40813-017-0057-2/FIGURES/1

Haritova, A. M., Rusenova, N. V, Parvanov, P. R., Lashev, L. D., & Fink-Gremmels, J. (2006). Pharmacokinetic-pharmacodynamic modelling of danofloxacin in turkeys. *Veterinary Research Communications, 30*(7), 775-789. doi: 10.1007/s11259-006-3400-7

Hart, B. L. (2009). Beyond fever: comparative perspectives on sickness behavior. *Encyclopedia of Animal Behavior, 1*, 205-210. doi: 10.1016/B978-0-08-045337-8.00133-9

Hoeltig, D., Rohde, J., Brunner, B., Hellmann, K., Grandemange, E., & Waldmann, K.-H. (2018). Efficacy of a one-shot marbofloxacin treatment on acute pleuropneumonia after experimental aerosol inoculation of nursery pigs. *Porcine Health Management, 4*(1), 1-10. doi: 10.1186/s40813-018-0089-2

Hossain, Md. A., Park, H., Jeong, K., Jang, Y. ho, Kim, D. G., Kang, J., & Lee, K. (2017). Pharmacokinetic and pharmacodynamic evaluation of marbofloxacin in pig against korean local isolates of *Actinobacillus pleuropneumoniae. BioMed Research International, 2017*(1), 2469826. doi: 10.1155/2017/2469826

Lees, P., & Shojaee Aliabadi, F. (2002). Rational dosing of antimicrobial drugs: animals versus humans. *International Journal of Antimicrobial Agents, 19*(4), 269-284. doi: 10.1016/S0924-8579(02)00025-0

Nedbalcova, K., Satran, P., Jaglic, Z., Ondriasova, R., & Kucerova, Z. (2006). Haemophilus parasuis and Glässer's disease in pigs: a review. *Veterinarni Medicina, 51*(3), 168-179. doi: 10.17221/5537-VETMED

Nedbalcova, K., Zouharova, M., & Sperling, D. (2019). Post-antibiotic effect of marbofloxacin,enrofloxacinandamoxicillin against selected respiratory pathogens of pigs. *Veterinarni Medicina, 64*(2), 67-77. doi: 10.17221/123/2018-VETMED

O'Connor, A. M., Totton, S. C., & Shane, D. (2019). A systematic review and network meta-analysis of injectable antibiotic treatment options for naturally occurring swine respiratory disease. *Journal of Swine Health and Production, 27*(3), 133-149. doi: 10.1017/S1466252320000031

Opriessnig, T., Giménez-Lirola, L. G., & Halbur, P. G. (2011). Polymicrobial respiratory disease in pigs. *Animal Health Research Reviews, 12*(2), 133-148. doi: 10.1017/S1466252311000120

Rossi, L., Turin, L., Alborali, G. L., Demartini, E., Filipe, J. F. S., Riva, F., Riccaboni, P., Scanziani, E., Trevisi, P., Dall'Ara, P., Dell'Anno, M., & Baldi, A. (2021). Translational approach to induce and evaluate verocytotoxic E. coli O138 based disease in piglets. *Animals, 11*(8), 1-17. doi: 10.3390/ani1108 2415

Sargeant, J. (2018). *Protocol for a systematic review on antibiotic for prevention in swine.* Guelph.

Schneider, M., Paulin, A., Dron, F., & Woehrlé, F. (2014). Pharmacokinetics of marbofloxacininpigsafterintravenousand intramuscular administration of a single dose of 8 mg/kg: dose proportionality, influence of the age of the animals and urinary elimination. *Journal of Veterinary Pharmacology and Therapeutics, 37*(6), 523-530. doi: 10.1111/jvp.12125

Sun, J., Xiao, X., Huang, R.-J., Yang, T., Chen, Y., Fang, X., Huang, T., Zhou, Y.-F., & Liu, Y.-H. (2015). In vitro dynamic pharmacokinetic/ pharamcodynamic (PK/PD) study and COPD of marbofloxacin against Haemophilus parasuis. *BMC Veterinary Research, 11*(1), 2-8. doi: 10.1186/ s12917-015-0604-5

Thomas, E., Grandemange, E., Pommier, P., Wessel-Robert, S., & Davot, J. L. (2000). Field evaluation of efficacy and tolerance of a 2% marbofloxacin injectable solution for the treatment of respiratory disease in fattening pigs. *The Veterinary Quarterly, 22*(3), 131-135. doi: 10.1080/01652176.2000.9695041

Vallé, M., Schneider, M., Galland, D., Giboin, H., & Woehrlé, F. (2012). Pharmacokinetic and pharmacodynamic testing of marbofloxacin administered as a single injection for the treatment of bovine respiratory disease. *Journal of Veterinary Pharmacology and Therapeutics, 35*(6), 519-528. doi: 10.1111/J.1365-2885.20 11.01350.X

Vilalta, C., Giboin, H., Schneider, M., Garch, F. el, & Fraile, L. (2014). Pharmacokinetic/ pharmacodynamic evaluation of marbofloxacin in the treatment of Haemophilus parasuis and Actinobacillus pleuropneumoniae infections in nursery and fattener pigs using Monte Carlo simulations. *Journal of Veterinary Pharmacology and Therapeutics, 37*(6), 542-549. doi: 10.1111/JVP.12134

Vilalta, C., Schneider, M., López-Jimenez, R., Caballero, J. M., Gottschalk, M., & Fraile, L. (2011). Marbofloxacin reaches high concentration in pig tonsils in a dose-dependent fashion. *Journal of Veterinary Pharmacology and Therapeutics, 34*(1), 95-97. doi: 10.1111/J.1365-2885.2010. 01206.X

Yang, F., Liu, Y., Li, Z., Wang, Y., Liu, B., Zhao, Z., Zhou, B., & Wang, G. (2017). Tissue distribution of marbofloxacin in pigs after a single intramuscular injection. *Journal of Veterinary Science, 18*(2), 169-173. doi: 10.4142/jvs.2017.18.2.169

Zou, M., & Zeng, Z. (2012). Efficacy of marbofloxacin against experimentally induced Actinobacillus pleuropneumoniae in swine. *Southwest China Journal of Agricultural Sciences, 25*(6), 2333-2337. doi: 10.1186/s40813-018-0089-2