Antibiotic sensitivities of fecal E. coli isolates from Austrian pigs

Sabine Elicker1 Louis Fischer2 Daniela Philadelphy1 Wolfgang Sipos1
1. University of Veterinary Medicine Vienna, Vienna, Austria; 2. Veterinary Practice Entenfellner, Stössing, Austria; 3. LaboVet GmbH, Vienna, Austria

Introduction

E. coli are the most frequent pathogens causing diarrhea in pigs. Besides diarrhea, they can also cause septicemias and cystitides. Suckling and weaned piglets most often suffer from diarrhea, whereas colitoxin shock is most often found in piglets short after weaning.

E. coli are gram-negative bacteria belonging to the family of Enterobacteriaceae. Classification is based on O-, K-, H-, and F-antigens. Additionally, E. coli are classified as enterotoxic (ETEC), enteropathogenic (EPEC), necrotoxic (NTEC), and shigatoxin-like producing (STEC) strains due to their pathogenic factors. STECs are further divided into enterohemorrhagic (EHEC) and edema disease causing (EDEC) strains (1).

Due to the clinical importance of these bacteria, large scale usage of antibiotics is the consequence. As antibiotic usage is an effective measure in the fight against bacterial infections if administered correctly on the one hand, but may lead to unfavourable side-effects such as increasing antibiotic resistance if given careless on the other hand (2), the following data aim at helping the practitioner in his decision which antibiotic to use.

Materials and Methods

E. coli isolates out of 444 pigs (24 suckling piglets, 314 weaners, 88 fattening pigs, and 13 sows) suffering from diarrhea were tested for their antibiotic sensitivities by routine agar diffusion test. Following antibiotic substances were included: amoxicillin, cefquinome, colistin, enrofloxacin, gentamicin, lincospectin, and sulfamethoxazole-trimethoprim.

Results

Isolates were most sensitive to cefquinome and enrofloxacin. Thus, bacterial growth could be inhibited at 98.8 % by cefquinome and at 89.9 % by enrofloxacin. Sensitivities to the other antibiotics were less pronounced (lincospectin: 60.7 %, sulfamethoxazole-trimethoprim: 54.9 %, gentamicin: 40.9 %, colistin: 36.2 %, amoxicillin: 21.0 %). Single isolates, which were additionally tested for their sensitivities against neomycin and tylosine, were completely resistant against these substances.

Additionally, differences in the susceptibilities were found concerning the source, i.e. the different age groups. 100 % of isolates derived from fattening and breeding animals were susceptible to cefquinome and 95.7 % of isolates from fattening pigs alone to enrofloxacin. Nevertheless, susceptibilities to gentamicin and amoxicillin were reduced (25.5 %, 14.9 %) in these animals. Isolates of sows were comparably highly susceptible to lincospectin (76.9 %) and those of suckling piglets to lincospectin, sulfamethoxazole-trimethoprim, and gentamicin (91.7 %, 87.5 %, 65.0 %). However, these age-dependent data are considered preliminary due to the small number of animals in the age groups of suckling piglets and sows.

Discussion

This study exhibited marked differences in the antibiotic susceptibility of fecal E. coli isolates. Importantly, isolates showed reduced sensitivities against the frequently applied substance colistin and also against the broad-spectrum antibiotic amoxicillin. Cefquinome and enrofloxacin were shown to be most effective against fecal E. coli isolates.

References

Metaphylaxis with butafosfan and vitamin B12 (Catosal®) in pregnant sows enhanced the immunity of new born piglets that resulted in improved weaning weight

Abdulkerim Deniz1 Supoj Watanapongchati2 Athipoo Nuntaprasert3
1. Bayer Animal Health, Monheim, Germany; 2. Bayer Thai Co., Ltd., Bangkok, Thailand; 3. Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand

Introduction

Immunmodulatory effect of the combination butafosfan and vitamin B12 (Catosal®) in sheep (1), calves (2) and mice (3) was already reported. Beneficial effect of Catosal® on metabolic function in the farrowing sows was also reported (4). The purpose of the present study was to investigate the effect of the metaphylactic treatment with Catosal® in pregnant sows on the immunoglobulines in colostrum and blood of sows and on newborn piglets. Furthermore, production parameters were also investigated.

Material and method

Thirty randomly selected pregnant crossbred sows were allocated into one of two study groups equally. All sows were managed and treated with same standard routine applications during the pregnancy. Catosal® group was treated with 20 ml of Catosal® (100 mg butafosfan and 0.05 vitamin B12/ml) at 3 weeks, 2 weeks and 1 week before farrowing start intramuscularly. And control group did not receive Catosal® but 20 ml saline. Colostrum and blood samples from all sows were collected at the start of farrowing to test the immunoglobulines (IgG, IgM, IgA). Blood was collected from new born piglets at 3 days of age to test above mentioned immunoglobulines (n=15 for each group). Farrowing and weaning performance of sows and piglets was evaluated. Commercial Indirect ELISA test kit (Bethyl Laboratories Inc., Montgomery, TX) for analysis of the total immunoglobulins (IgG, IgM, IgA) in the colostrums and blood was used. Plasma and colostral samples were diluted at 1:10,000 for the analysis. All piglets in the study groups had standard routine treatments. Data were analyzed statistically based on Wilcoxon-Mann-Whitney-U Test, two sided, 95% CI.

Results

Mean number of alive born piglets in Catosal and control group litters was 10.8 and 10.9 respectively. Metaphylaxis with Catosal® had significant beneficial effect for the immunity (Table 1) and weaning weight of liveborn piglets (Figure 1). There was an increase by 6% (534 g) in the weaning weight of liveborn piglets in the Catosal group compared to control group (p<0.05). An increase (2.6%) in the survivability of alive born piglets up to weaning was observed in the Catosal group (91.4%), but this increase could not be proven statistically. In the first week of life, piglets in Catosal® group had better fecal consistency, low diarrhoea incidence.

Conclusion

Metaphylaxis with Catosal® at prepartum period stimulated the immunity of sows that resulted in increased immunoglobulines in colostrum and consequently in piglets. An increased weaning weight was a significant economic benefit of the treatment.
Pharmacokinetic / Pharmacodynamic Relationships of Valnemulin (Econor®) and Lawsonia intracellularis the Cause of 'Ileitis'

David G. Burch1 Ulrich Klein2
1. Octagon Services Ltd, Old Windsor, Berkshire, UK; 2. Novartis Animal Health Inc., Basel, Switzerland

Introduction
Valnemulin (Econor® - Novartis Animal Health Inc.), a pleuromutilin with exceptional activity against the gut pathogens Brachyspira hyodysenteriae and B. pilosicoli was reported to have good activity against Lawsonia intracellularis (Li), (1) the causal agent of Porcine Proliferative Enteropathy or 'ileitis'. Valnemulin (VAL) has been shown to be highly effective in the treatment of ileitis (1) when given in feed. It was the purpose of this paper to look at the pharmacokinetics (PK) of VAL in the gut contents and relate these to the pharmacodynamics (PD) of VAL and its clinical effect against Li.

Materials and Methods
A) Pharmacokinetics (PK)
VAL concentrations were described in colon contents (2) following in feed medication at approximately 75 and 200 ppm for 28 days at 1.6 and 5.2μg/g. The relationship between colon and ileum contents was modelled (3) and it was estimated that an effective steady state concentration of approximately 29% of the colon contents was found in the ileum. These figures were used to determine the ileum contents concentration of VAL at 0.49 and 1.5μg/ml, respectively.

B) Pharmacodynamics (PD)
A recent report (4) showed that VAL had a very low intracellular MIC 90 against 10 isolates of Li from the United States (n=6) and Europe (n=4), at ≤0.125μg/ml. This level was much lower than previously reported (1) at <2μg/ml. The in vitro method was slightly different and used McCoy cells rather than rat enterocytes (IEC-18 cells) to grow the Li. They also used a wider range of different concentrations (0.125-128μg/ml) than the original study, making a titration of low and high MICs possible.

C) Clinical effect
In an artificial challenge trial (1), VAL was given in feed at 25, 37.5 & 50 ppm, from 2 days before challenge with Li strain LR189/5/83, with an intracellular MIC of <0.125μg/ml, until termination 21 days after infection. In the treatment challenge study (1), VAL was given 7 days after infection for 14 days until termination (see Table 1).

Lesions in the ileum were examined grossly and histologically.

Results and Discussion
Effective concentrations of VAL are achieved in the ileum contents, which inhibited the development of gross lesions of ileitis at 50 ppm. At 75 ppm VAL and above, no gross or microscopic lesions were observed (see Figure 1 & 2) following treatment.

Table 1: Necropsy results (ileum) of the prevention (25, 37.5 & 50 ppm) and treatment (75 & 125 ppm) trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Gross lesions</th>
<th>Micro lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected control</td>
<td>5/7</td>
<td>6/7</td>
</tr>
<tr>
<td>VAL 25ppm (P)</td>
<td>2/7</td>
<td>6/7</td>
</tr>
<tr>
<td>VAL 37.5ppm (P)</td>
<td>1/5</td>
<td>2/5</td>
</tr>
<tr>
<td>VAL 50ppm (P)</td>
<td>0/7</td>
<td>1/7</td>
</tr>
<tr>
<td>VAL 75ppm (T)</td>
<td>0/7</td>
<td>0/7</td>
</tr>
<tr>
<td>VAL 125ppm (T)</td>
<td>0/7</td>
<td>0/7</td>
</tr>
</tbody>
</table>

References
Effect of Catosal® on appetite and body weight of sows during lactation

Eliana O. Dantas1 Rogério B. Petri1 Stefan A. Rohr2
1. Bayer S.A., São Paulo, Brazil; 2. Integrall Consulting, Belo Horizonte, MG, Brazil

Introduction
Weight loss by the sow should not be more than 12% during lactating period, which will support good piglet assistance, a fast return to heat after weaning and a good reproductive performance in the subsequent parturition (1). The aim of this trial was to evaluate the impact of Catosal® (Butaphosphophan 100mg and Cyanocobalamin 0,05mg/mL; Bayer Animal Health; in some countries available as Catosal®B12, Coforta® or Phosphorum®B12) in lactating sows on different parameters, including feed intake and weight loss during lactation period.

Materials and Methods
The experiment was conducted in a Brazilian commercial farm including 360 sows which were equally distributed in blocks according to the parturition order: first parturition, second parturition, and between third and sixth parturition. These blocks were distributed into four treatments, with 90 repetitions, and each animal was considered an experimental unit. Around 110 days of gestation the sows were transferred to the farrowing facility and received the lactation diet in the restricted amount of 2.0 kg/day. After farrowing, feed was distributed twice in a day, ad libitum. The wet feed consisted of 58% feed and 42% water. Sows were weighted in the entrance and in the exit of the farrowing unit, and the feed intake was measured daily. The weaning was proceeded when piglets were 21 days old. The treatment groups were classified as: T1 (negative control), T2 (10mL of Catosal®), T3 (15mL of Catosal®) and T4 (20mL of Catosal®). The product was administered intramuscularly after detection of the first signals of parturition.

Results
Average weekly feed intake was high for all treatments in the first lactation week. However, the T4 group had statistically higher average feed intake (p<0.05) than the control group T1 on lactation week 1, 2 and 4 (Table 1) as well as total feed consumption during lactation of T4 was significantly higher than T1. For absolute values of weight loss, it was observed that the T4 group had a lower weight loss with statistical significance (p<0.05) than the groups T1 and T2. The T3 group also had a lower weight loss with statistical significance than the group T1. For the percentages of weight loss, only the T4 group had a lower weight loss with statistical significance (p<0.05) than the groups T1 and T2.

Discussion
Sows that received 15 and 20 mL of Catosal® at farrowing had lower weight loss during the suckling period with a difference from T1 such as 3.21 kg and 5.14 kg respectively. This fact is clearly associated with an increased feed intake (appetite) in these treatment groups. Catosal® application at farrowing stimulates the appetite of sows during lactation and prevents from weight loss at the critical time point where sows should feed newborn piglets.

References
**Effect of butaphosphan+vitamin B12 (Catosal®/Coforta®) on pig performance**

Eijalin Z. Bautista1 Zoilo M. Lapus2, 4, 3 Jomer B. Fule1 Serafin Jr L. Garciano1

1. Bayer Philippines Inc., Laguna, Philippines; 2. Philippine College of Swine Practitioners, Quezon City, Philippines; 3. Asian Pig Veterinary Society, Quezon City, Philippines; 4. Swine Consultant, Quezon City, Philippines

**Introduction**

In intensive pig production systems, pigs are exposed to multiple stressors such as handling, mixing with unfamiliar conspecifics, and movement to other buildings, all of which may adversely affect performance of the animals. Stress causes the release of catabolic hormones like cortisol which can negatively affect metabolism, leading to reduced weight gain in these growing animals (Ekkel et al., 1995). Coforta®/ Catosal® is a metabolic stimulant and tonic supplement containing 100 mg butaphosphan and 0.05 mg of cyanocobalamin per ml as active ingredients. It has been reported to reduce stress by reducing cortisol levels (van der Staay et al., 2006; de Groot et al., 2003). This field study aimed to investigate the effects of Catosal® on the weight gain of pigs when given strategically during stressful periods such as handling, movement and transfer to other buildings.

**Materials and Methods**

This field study was conducted in a 300 sow level farm. Twenty clinically healthy, purebred sows and their piglets were divided into two groups, the treatment group (N= 108 piglets), and control group (N=111 piglets). In the treatment group, the sows received two injections of Catosal® at 20 ml per dose once at the start of farrowing and the second dose 28 days post-farrowing (weaning day). The corresponding piglets were given Catosal® at the following dosages and schedules: 1 ml at day 3 of age, coinciding with the administration of iron dextran and toltrazuril 0.4 ml/ kg; 1 ml at day 28 (weaning day); 2 ml when the piglets were transferred from the farrowing building to the flat deck, and 5 ml upon transfer from the flat deck to the grower buildings.

The sows and piglets from the control group remained untreated with any preparation similar to Catosal®, nor with a placebo, apart from a single dose of Catosal® given to the piglets at 10 days of age, which was the usual farm program.

All piglets were weighed at birth, at weaning, during transfers and upon market.

**Results and Discussion**

The pigs in the Catosal® group had significantly higher average daily gain (ADG) in the different stages of production compared to the control group. Even by adjusting weight gain at 40 days and 80 days of rearing period in the flat deck and grower-finisher buildings, respectively, and at 150 days birth-to-market rearing period in order to have an equal basis of comparison, weight gain was significantly higher in the group from post-weaning until market. By the end of the trial, the ADG of the Catosal® group was higher by 58 grams per day, which translated to an average of 8.5 kilogram-difference in the weight gain of the Catosal® group.

**Table 1.**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Catosal</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ave. birth weight (kg)</td>
<td>1.50 (N= 111)</td>
<td>1.55 (N=108)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Ave. birth weight upon transfer to flat deck (kg)</td>
<td>13.66 (N=96)</td>
<td>15.31 (N= 96)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ave. daily weight gain (ADG) flat deck (kg)</td>
<td>0.547</td>
<td>0.627</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adjusted weight gain for 40-day rearing period in the flat deck (kg)</td>
<td>21.90</td>
<td>25.08</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ave. weight upon transfer to the grower building (kg)</td>
<td>35.7 (N= 96)</td>
<td>40.52 (N= 96)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ADG grower-finisher (kg)</td>
<td>0.761</td>
<td>0.831</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adjusted weight gain for 80-day rearing period in the grower-finisher building (kg)</td>
<td>60.90</td>
<td>66.50</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ave. market weight (kg)</td>
<td>92.49 (N= 96)</td>
<td>102.01 (N= 94)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ave. market age</td>
<td>174.32</td>
<td>173.23</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>ADG day 0 to market (kg)</td>
<td>0.523</td>
<td>0.581</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Adjusted weight gain at 150 days (kg)</td>
<td>78.44</td>
<td>87.09</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Conclusions**

In this field trial, Catosal® given to pigs during stressful periods in production resulted to a significantly increased daily weight gain and market weight of pigs. This resulted, based on the return on investment calculation, to high profitability for the farmers (17.02 USD per head under Philippine conditions). There were no treatment-related side effects neither in piglets nor in pigs.

**References**

Clinical efficacy of acetyl-salicilic acid as an adjunct to the antibacterial treatment of porcine respiratory disease

Lorenzo Fraile1 Carles Vilalta1 Rosa López-Jimenez1 Maria Teresal L. Varela2
Sergio Lopez-Soria1 Miquel Nofrarias1 Tomás Alcala3 Sonia Espín4
1. CReSA, Bellaterra, Spain; 2. Laboratorios SYVA, León, Spain; 3. Departamento de Métodos Estadísticos, Zaragoza, Spain; 4. Explotacions Agrícoles i Ramaderes S.L, Bellcaire d’urgell, Spain

Introduction
Infection and environmental conditions make inflammation a manifestation of respiratory disease in pigs that decrease the ability of the lungs to exchange gases. In fact, the inflammatory response may become so overwhelming as to be life threatening in itself (1, 2).

The benefits of therapeutic intervention with non-steroidal anti-inflammatory drugs (NSAIDs) are because of their properties as inhibitors of the actions, synthesis or release of inflammatory mediators. In addition, one of the effects of NSAIDs, such as acetylsalicylic acid (AAS), is to act as antipyretics, improve the general clinical status of animals and increase food and water intake. The aim of this study was to investigate the clinical efficacy of AAS as an adjunct to the antibacterial treatment of porcine respiratory disease.

Material and Methods
142 piglets of 4 months of age were divided in two groups (experimental and control group). These animals were suffering a respiratory disease. The inclusion criteria was the presence of pyrexia (>39.7 °C) in the animals. Experimental group (A) received Doxycycline hyclate and AAS by drinking water at a dose of 10 mg/Kg (doxiporc®, Laboratorios Policherm, Spain) and 100 mg/kg of body weight (febrina porcino®, Laboratorios SYVA, Spain) for five consecutive days, respectively whereas control group (B) received only the antibiotic treatment. The animals were clinically examined before treatment (day 1) and at 2, 3, 4, 5 and 6 days after treatment for rectal temperature (°C) and abdominal breathing, cough and depression. Each parameter was scored using a scale of 0 = normal, 1 = slight or moderate and 2 = severe according to Moore et al. (1986). A statistical analysis was performed by paired t-test using the statistical software SPSS System v15. The alpha level used for determination of significance for all analyses was P < 0.05.

Results
The experimental group showed always a mean temperature lower than the negative control group (group B) throughout the trial (see figure) and this fever decrease for animals receiving AAS (group A) is statistically significant at days 2, 5 and 6 of the trial (p<0.05) in comparison with animals not receiving AAS (group B). However, it was not observed significant differences for respiratory symptoms throughout the trial between both groups.

Discussion
NSAIDs are used to block the production and/or the effects of inflammatory mediators and modulators which may have a deleterious effect on alveolar exchange of gases (3). Results support the idea that AAS is an effective adjunct in the treatment of porcine respiratory disease complex to decrease fever. However, we did not observe a synergic effect to decrease respiratory symptoms in animals receiving antibiotic and AAS. Nevertheless, it was not possible to check the lung inflammation to observe the anti-inflammatory effect at lung level as observed in bovine for other NSAIDs (4).

References
2. Friton et al, 2005 Veter. record 156: 809-811
PK and PK/PD of Pharmasin® 250 mg/g Premix (tylosin phosphate) following multiple oral administration in pigs

Mariana Karanikolova1 Stela Vesselova1 Valeri Nazarov1 Stanislava Ivanova1 Dimitar Pashov2 Spas Petkov3 Alain Kanora3
1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Department of Pharmacology, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria; 3. Huvepharma NV, Antwerp, Belgium

Introduction
In this study we determined some pharmacokinetic (PK) parameters of tylosin as Pharmasin® 250 mg/g Premix (Huvepharma NV) and related these to its pharmacodynamic (PD) with a view to a substantiated clinical use.

Materials and Methods
Eleven mixed breed pigs, weighing 20–25kg without a history of macrolide administration were enrolled in the study. Ten animals, equally male and female, received tylosin (as phosphate) at 10 mg/kg BW / 24h (Pharmasin® 250 mg/g Premix) via feed offered ad libitum prepared daily at 6.00 am for 5 consecutive days. During the treatment 40 heparinized blood samples were obtained from each pig at predetermined intervals. One pig received no drugs and served as negative control. On the 5th day the treated pigs were euthanized: 2 animals at each of the 5 different time points. Blood, organ and tissue samples from respiratory and GI tract were collected. Plasma and organ (tissue) tylosin concentrations were measured by validated HPLC method.

Results
The plasma concentration-time profile of tylosin showed nearly identical daily courses within the treatment period (Fig. 1).

There were no significant differences between the 4 daily peak concentrations (C_{max}) and between C_{min} or AUC values (Repeated measures ANOVA post hoc test). However, the individual plasma concentration data were quite variable and showed that in 70% of the animals, steady state was reached at 54.4±7.7 h after administration initiation. After 4 days of treatment C_{max-ss} was 0.55±0.04 μg/mL, C_{min-ss} 0.30±0.03 μg/mL, C_{av-ss} 0.42±0.03 μg/mL and AUC_{0-24h} 10.14±0.84 μg h/mL. Steady state tylosin concentrations in lung tissue and bronchial mucosa and secretions peaked 4h after the 5th administration, being 0.95±0.05 μg/g and 1.09±0.06 μg/g, respectively, and persisted to the last sampling point (12thh) being 0.85±0.06 μg/g and 0.97±0.04 μg/g, respectively. The corresponding tissue/plasma ratios of AUC were 1.81 and 2.04.

Discussion and Conclusion
The mean plasma steady state values of C_{min-ss} and of C_{max-ss} were higher than the MIC_{90} described for clinically important porcine bacterial pathogens of respiratory tract: M. hyopneumoniae – 0.25 μg/mL1, E. rhusiopathiae – <0.13 μg/mL3, Leptospira spp. – 0.06 μg/mL3. This was valid also for organ (tissue) steady state concentrations in respiratory tract which were higher than those in plasma. The concentration in ileal and colonic content provided active levels against L. intracellularis – MIC_{90}=4 μg/mL2 and some sensitive strains of B. hyodysenteriae – MIC_{90}=16>256 μg/mL2. The efficacy PK–PD breakpoint of macrolide antibiotics is a time above the MIC (T>MIC) of 50–80% of dosage interval4. In this study active tylosin antimicrobial levels persisted throughout the period of administration. Therefore, tylosin phosphate as Pharmasin® 250 mg/g Premix at the dosage schedule tested complies with the requirements of PK–PD approach. This supports its clinical use in the control of respiratory and gastrointestinal infections.

References
Pharmacokinetics of Pharmasin™ 250 mg/g Premix (tylosin phosphate) following single oral administration in pigs

Mariana Karanikolova1 Stela Vesselova1 Valeri Nazarov1 Stanislava Ivanova1 Dimitar Pashov2 Spas Petkov1 Alain Kanora3
1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Department of Pharmacology, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria; 3. Huvepharma NV, Antwerp, Belgium

Introduction
Tylosin is a macrolide antibiotic that acts mostly against Gram-positive bacteria and mycoplasma. Although it has been used in veterinary medicine for a long time the data on its pharmacokinetic (PK) properties in pigs are incomplete. This study aimed at providing PK data of tylosin as Pharmasin™ 250 mg/g Premix (Huvepharma NV) that could aid PK-pharmacodynamic (PD) integration as a rational base for its clinical use.

Materials and Methods
Six healthy pigs, equally male and female, weighing 20–25 kg without a history of macrolide administration were enrolled in the study. The animals received by intubation a single p.o. dose of tylosin (as phosphate) 10 mg/kg BW (Pharmasin™ 250 mg/g Premix), as water suspension. Heparinized blood samples (n=13 per animal) were taken at predetermined intervals. Plasma tylosin concentrations were measured by a validated HPLC method. The results obtained for tylosin disposition were tested by compartmental method (using Akaike’s information criterion) and by non-compartmental approach as well.

Results
Plasma concentration vs. time data best fitted applying the non-compartmental model. The highest plasma concentration ($C_{max}$ = 1.08±0.08 μg/mL) was achieved 2h post administration. Thereafter, plasma levels declined remaining higher than 0.38±0.017 μg/mL at 12h post administration (Fig. 1). The half-life ($t_{1/2}$) was 6.66h. $AUC_{0-12h}$ and $AUC_{0-∞}$ were 8.2±0.49μg.h/mL and 11.84±0.58μg.h/mL, respectively (Table 1).

Discussion and Conclusion
The elimination half-life of tylosin, calculated after single oral dose (6.66h), was higher than that reported after i.v. injection (4.5h)2 and the peak plasma concentration was comparable to the one found after i.m. injection (1.0 μg/mL)2. Throughout the period of determination plasma tylosin levels were higher than the MIC90 described for clinically important porcine bacterial pathogens: *Mycoplasma hyopneumoniae* - 0.25 μg/mL1, *Erysipelothrix rhusiopathiae* - <0.13 μg/mL3, *Leptospira spp.* – 0.06 μg/mL3. A primary precondition in PK–PD approach for the effectiveness of macrolide antibiotics is a time above the MIC (T>MIC) of 50–80% of dosage interval4. The results of this study show that tylosin PK at the dosage schedule tested complies with this requirement and can ensure therapeutically effective concentrations throughout the 12h period of determination. This supports clinical use of tylosin phosphate as Pharmasin™ 250 mg/g Premix in the control of respiratory and gastro-intestinal infections.

References
PK and PK/PD of Pharmasin® 100% w/w WSG (tylosin tartrate) following multiple oral administration in pigs

Stela Vesselova1 Mariana Karanikolova1 Valeri Nazarov1 Stanislava Ivanova1 Dimitar Pashov2 Spas Petkov3 Alain Kanora3
1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Department of Pharmacology, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria; 3. Huvepharma NV, Antwerp, Belgium

Introduction

In this study we investigated the pharmacokinetic (PK) behavior of tylosin as Pharmasin® 100% w/w WSG (Huvepharma NV) in pigs in order to explore PK–pharmacodynamic (PD) integration as rational basis for its clinical use.

Materials and Methods

Eleven mixed breed pigs, weighing 20–25 kg without a history of macrolide administration were enrolled in the study. Ten animals, equally male and female, received tylosin (as tartrate) at 10 mg/kg BW / 24h (Pharmasin® 100% w/w WSG) as medicated drinking water offered *ad libitum* daily freshly prepared at 6.00 am for 5 consecutive days. During the treatment 40 heparinized blood samples were obtained from each pig at predetermined intervals. One pig did not participate and served as negative control. On the 5th day the treated pigs were euthanized: 2 animals at each of the 5 different time points. Blood, organ and tissue samples from respiratory and GI tract were collected. Plasma and organ (tissue) tylosin concentrations were measured by validated HPLC method.

Results

The plasma concentration-time profile of tylosin showed nearly identical daily courses within the treatment period (Fig. 1).

There were no significant differences between the 4 daily peak concentrations (Cmax) and between Cmin or AUC values (Repeated measures ANOVA Scheffe post hoc test). However, the individual plasma concentration data were quite variable and showed that in 70% of the animals steady state was reached at 46.9±6.33 h after treatment initiation. After 4 days treatment Cmax was 0.58±0.04 μg/mL, Cmin was 0.28±0.03 μg/mL, CSS was 0.45±0.04 μg/mL, and AUC0-24h was 10.73±0.92 μg.h/mL. Steady state tylosin concentrations in lung tissue and bronchial mucosa and secretions peaked 2h after the 5th administration, being 0.93±0.06 μg/g and 1.06±0.06 μg/g, respectively, and persisted to the last sampling point (12thh), being 0.67±0.12 μg/g and 0.78±0.13 μg/g, respectively. The corresponding tissue/plasma ratios of AUC were 1.88 and 2.17.

Discussion and Conclusion

The mean plasma steady state values of Cmin and of CSS were higher than the MIC90 described for clinically important porcine bacterial pathogens of respiratory tract: M. hyopneumoniae ~ 0.25 μg/mL, E. rhusiopathiae ~ 0.13 μg/mL, Leptospira spp ~ 0.06 μg/mL. This was valid also for organ (tissue) steady state concentrations in respiratory tract which were higher than those in plasma. The concentration in ileal and colonic content provided active levels against *L. intracellularis* – MIC90 = 4 μg/mL2 and some sensitive strains of *M. hyopneumoniae*. Generally, PK–PD breakpoint for clinical and bacteriological efficacy of macrolide antibiotics is a time above the MIC (T>MIC) of 50–80% of dosage interval4. In this study active tylosin antimicrobial levels persisted throughout the period of administration. Therefore, tylosin tartrate as Pharmasin® 100% w/w WSG at the dosage schedule tested complies with the requirements of PK–PD approach. This supports its clinical use in the control of respiratory and gastro-intestinal infections.

References


<table>
<thead>
<tr>
<th>Parameters, units</th>
<th>Blood plasma</th>
<th>Lung tissue</th>
<th>Bronchial mucosa</th>
<th>Ileum wall</th>
<th>Ileal content</th>
<th>Colon wall</th>
<th>Colonic content</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-12h, μg.h/mL (g)</td>
<td>5.19</td>
<td>9.75</td>
<td>11.28</td>
<td>2.87</td>
<td>288.55</td>
<td>38.36</td>
<td>816.85</td>
</tr>
<tr>
<td>Cmax, μg/mL (g)</td>
<td>0.65</td>
<td>0.93</td>
<td>1.06</td>
<td>0.29</td>
<td>27.2</td>
<td>4.05</td>
<td>76.7</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>8.0</td>
<td>4.0</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>C12thh, μg/mL</td>
<td>0.32</td>
<td>0.67</td>
<td>0.78</td>
<td>0.24</td>
<td>20.8</td>
<td>2.48</td>
<td>71.3</td>
</tr>
<tr>
<td>MRT, h</td>
<td>14.1</td>
<td>17.0</td>
<td>16.2</td>
<td>13.1</td>
<td>18.0</td>
<td>13.6</td>
<td>11.1</td>
</tr>
<tr>
<td>T/P1 ratio of Cmax</td>
<td>NC</td>
<td>1.43</td>
<td>1.63</td>
<td>0.45</td>
<td>41.8</td>
<td>6.23</td>
<td>118.0</td>
</tr>
<tr>
<td>T/P1 ratio of C12thh</td>
<td>NC</td>
<td>2.09</td>
<td>2.44</td>
<td>0.75</td>
<td>65.0</td>
<td>7.75</td>
<td>222.8</td>
</tr>
</tbody>
</table>

*Bronchial mucosa and secretions; †Tissue/Plasma; NC, Not Calculated (each datum represents mean of 2 animals).
Pharmacokinetics of Pharmasin® 100% w/w WSG (tylosin tartrate) following single oral administration in pigs

Stela Vesselova¹ Mariana Karanikolova¹ Valeri Nazarov¹ Stanislava Ivanova¹ Dimitar Pashov² Spas Petkov³ Alain Kanora³
¹ 1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Department of Pharmacology, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria; 3. Huvepharma NV, Antwerp, Belgium

Introduction

Tylosin is a macrolide antibiotic that acts mostly against Gram-positive bacteria and mycoplasma. Although it has been used in veterinary medicine for a long time the data on its pharmacokinetic (PK) properties in pigs are incomplete. The aim of this study was to obtain PK data intended to facilitate PK–pharmacodynamic (PD) integration in clinical use of tylosin as Pharmasin® 100% w/w Water Soluble Granules (Huvepharma NV).

Materials and Methods

Six healthy pigs, equally male and female, weighing 20–25 kg without a history of macrolide administration were enrolled in the study. The animals received by intubation a single p.o. dose of tylosin (as tartrate) 10 mg/kg BW (Pharmasin® 100% w/w Water Soluble Granules), dissolved in water. Heparinized blood samples (n=13 per animal) were taken at predetermined intervals. Plasma tylosin concentrations were measured by a validated HPLC method. The results obtained for tylosin disposition were tested by compartmental method (using Akaike’s information criterion) and by non-compartmental approach as well.

Results

Plasma concentration vs. time data fit best by applying the non-compartmental model. The highest plasma concentration (Cmax = 1.10±0.08 μg/mL) was achieved 2h post administration. Thereafter, plasma levels declined remaining higher than 0.31±0.2 μg/mL at 12h post administration (Fig. 1). The half-life (t1/2 β) was 5.6±0.08h;5.59* and t1/2β* were 7.79±0.58 μg.h/mL and 10.31±0.75 μg.h/mL, respectively (Table 1).

Table 1. Pharmacokinetic parameters of tylosin in pigs following single oral dose of 10 mg/kg BW

<table>
<thead>
<tr>
<th>Parameters, units</th>
<th>Tylosin, 10 mg/kg BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>β (h⁻¹)</td>
<td>0.124±0.002</td>
</tr>
<tr>
<td>t1/2β (h)</td>
<td>5.6±0.08h;5.59*</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>1.1±0.08</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.0±0</td>
</tr>
<tr>
<td>AUC0-tlast (μg.h/mL)</td>
<td>7.79±0.58</td>
</tr>
<tr>
<td>AUC0-∞ (μg.h/mL)</td>
<td>10.31±0.75</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>8.69±0.1</td>
</tr>
<tr>
<td>tlast (h)</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Harmonic mean, each datum represents the mean ± SEM

Discussion and Conclusion

The elimination half-life of tylosin, calculated after single oral dose (5.6h), was higher than that reported after i.v. injection (4.5h) and the peak plasma concentration was comparable to this found after i.m. injection (1.0 μg/mL). Throughout the period of determination plasma tylosin levels were higher than the MIC90 described for clinically important porcine bacterial pathogens: Mycoplasma hyopneumoniae – 0.25 μg/mL, Erysipelothrix rhusiopathiae – <0.13 μg/mL, Leptospira spp. – 0.06 μg/mL. According to PK–PD approach the breakpoint for clinical effectiveness of macrolide antibiotics is a time above the MIC (T>MIC) of 50–80% of dosage interval. The results of this study show that tylosin PK at the dosage schedule tested complies with this requirement and can ensure therapeutically effective concentrations throughout the 12h period of determination. This supports clinical use of tylosin tartrate as Pharmasin® 100% w/w Water Soluble Granules in the control of respiratory and gastro-intestinal infections.

References

Efficacy of flavomycin to susceptibility of haemolytic Escherichia coli in weaner to finishing pigs

Nuvee Prapasarakul1 Waree Niyomtuma1 Prapipat Khemsapb 2 Suthatip Prapatsornpinyo 3
1. Department of Veterinary Microbiology, Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand; 2. Huvepharma (Thailand) Ltd., Bangkok, Thailand; 3. Panuspokphand Pig Farm Co., Ltd., Chonburi, Thailand

Introduction

Escherichia coli is regarded as a commensal and opportunistic pathogen of gastrointestinal tract. α-haemolytic E. coli (HEC) is clearly more potential to induce pathogenic lesion due to possessing of exotoxins (4) This causes colibacillosis and oedema disease and directly impacts to severe economic loss (5)

In Thai pig industrial, intensive use of antimicrobials is a common alternative for control of infectious diseases. There has been a dramatically increasing of resistant bacteria against antimicrobials such as beta-lactams, macrolides, fluoroquinolones, tetracyclines and lincosamides because of use of different several antimicrobials during production periods other than 2 weeks prior to slaughter. However, not only pathogenic bacteria are affected from the administration, but also enteric commensal may rise up the risk of resistance in farm-level (6). Flavomycin is phosphoglycolipid antibiotic in flavophospholipal group that has been approved as a feed additive. It is active against Gram’s positive bacteria and also inhibits in vitro conjugation of Gram’s negative bacteria such as E. coli.

The current study was to evaluate minimal inhibitory concentration (MIC) to 6 antimicrobials of E. coli derived from weaner to finishing pigs that received flavomycin as a feed additive. We also determined an efficacy of flavomycin to 30 enterotoxigenic E. coli (ETEC) isolated from piglets.

Materials and Methods

Sample collection. 10 ppm of flavomycin was the addition of routine feed additive during 10 to 21 weeks of pig ages. Pig feces were collected and contained in transport media.

Bacteria. 30 ETEC isolated from piglets with colibacillosis since 2008, were derived from stock isolates of Dept Vet Micro. 63 E. coli comprising with 30, 16 and 17 isolates that were collected at 5, 15 and 25 week age, respectively. Haemolytic traits on 5% sheep blood agar were used for colony selective criteria. When HEC was not observed on the primary plate, non-HEC would be selected for MIC determination.

MIC determination. 6 antimicrobials comprising with flavomycin, colistin, chlorotetracycline, enrofloxacin, amoxicillin and oxacillin were used. Broth micro-dilution was carried out according to the recommendation of CLSI (2, 3).

Results and Discussion

Range of MIC distribution is shown in Fig 1. The MIC values of 30 ETEC against amoxicillin, oxacillin, and chlorotetracycline, were over 256 ug/ml. They were inhibited by flavomycin at 4-32 ug/ml. Enrofloxacin and colistin were the effective agents to the tested E. coli.

HEC was mostly isolated from the period before adding of flavomycin and were disappeared in pig aged 15 week. The MIC50 of each batch of isolation is compared in Table 1.

Table 1 Presence of isolation rate and MIC50 of each batch

<table>
<thead>
<tr>
<th>Isolation</th>
<th>Pig ages (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>HEC</td>
<td>28</td>
</tr>
<tr>
<td>Non-HEC</td>
<td>2</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td></td>
</tr>
<tr>
<td>colistin</td>
<td>0.5</td>
</tr>
<tr>
<td>enrofloxacin</td>
<td>0.5</td>
</tr>
<tr>
<td>flavomycin</td>
<td>4</td>
</tr>
<tr>
<td>chlorotetracycline</td>
<td>256</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>512</td>
</tr>
<tr>
<td>oxacillin</td>
<td>512</td>
</tr>
</tbody>
</table>

The MIC of 63 isolates was consistent to that of ETEC in 2008. beta lactam resistant bacteria may be a native clone in the area of study. Flavomycin clearly reduced HEC in fattening pigs and its susceptibility was lower in the final week. These confirmed a direct efficacy to pathogenic agents (1) and may be able to maintain susceptible level from weaner to finishing.

Acknowledgement

We thank Meiji pharmaceutical Co. Ltd. (Thailand) for providing colistin sulfate.

References

2. CLSI, 2006. CLSI M7-A7., Wayne, PA.
3. CLSI, 2008. CLSI M100-S18., Wayne, PA.
6. Harada et al., 2008 Microb Drug Resist 14, 239.
Pharmacokinetic/pharmacodynamic relationships of HydroDoxx® 500 mg/g Powder (doxycycline) in porcine respiratory disease complex (PRDC)

Mariana Karanikolova1 Stela Vesselova1 Valeri Nazarov1 Spas Petkov2 Koen De Gussem2 Alain Kanora2
1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Huvepharma NV, Antwerp, Belgium

Introduction

The porcine respiratory disease complex (PRDC) is a leading cause of animal and economic losses in swine production6. Because bacteria are involved in this condition, antibiotics are a short-term measure in a multifaceted strategy of disease control. In the swine industry, tetracyclines have been applied particularly for respiratory tract infections7. Doxycycline (DOX) is a semi-synthetic tetracycline and a broad-spectrum bacteriostatic antibiotic against Gram-negative and Gram-positive aerobic and anaerobic bacteria, Rickettsiae, Chlamydiae, mycoplasmases and some protozoa10. DOX is characterized by a better lipid solubility, greater tissue penetration, improved antimicrobial activity and a different pharmacokinetic profile1,2. The objective of this paper was to review existing literature data on pharmacokinetic (PK) and pharmacodynamic (PD) properties of DOX with a view to evaluate their relationships as a base for its clinical effect in PRDC as HydroDoxx® 500 mg/g Powder for use in drinking water.

Pharmacokinetics

The multiple oral administration of DOX at 6.6, 11.5 and 12.9 mg/kg BW daily produces steady-state concentrations of respectively 0.37-0.89, 0.56-0.87 and 0.71-1.14 μg/mL9. In another experiment steady-state plasma levels ranging between 0.9 and 1.5 μg/mL have been observed during 8-day oral medication at a dosage regimen of 11.8-13.3 mg/kg/day5. Administration via drinking water at 10 mg/kg daily for 5 days results in mean plasma concentration at steady-state of 1.37±1.21 μg/mL10.

Pharmacodynamics

It was reported that MIC values of DOX for important porcine bacterial respiratory tract pathogens are 0.25 to 0.5 μg/mL8. In other studies, further values were determined3,10 (Table 1).

Table 1. MIC values bacterial respiratory tract pathogens

<table>
<thead>
<tr>
<th>Porcine pathogens</th>
<th>MIC50 values, μg/mL</th>
<th>MIC90 values, μg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. hypopneumoniae (Mh)</td>
<td>0.1 (10)</td>
<td>0.2 (10); 1.0 (3)</td>
</tr>
<tr>
<td>P. multocida (Pm)</td>
<td>0.106 (10)</td>
<td>0.517 (10); 1.0 (3)</td>
</tr>
<tr>
<td>B. bronchiseptica (Bb)</td>
<td>0.039 (10)</td>
<td>0.053 (10)</td>
</tr>
<tr>
<td>A. pleuropneumoniae (Ap)</td>
<td>1.422 (10)</td>
<td>2.387 (10); 2.0 (3)</td>
</tr>
</tbody>
</table>

PK-PD integration

Steady-state DOX plasma levels determined after oral medication with DOX at a dose of 11.5 mg/kg BW daily exceed MIC values 0.25 to 0.5 μg/mL2. In conformity with the type of its antimicrobial action, DOX belongs to concentration-time dependent (co-dependent) drugs with integrated PK-PD variables AUC/MIC and T>MIC with proposed values of 125 h and 50-80%. Based on this principle and analyzing the results obtained after 5-day administration of DOX via drinking water at a dose of 10 mg/kg daily other authors assume that the calculated mean values of (AUCSS/MIC90) 24h and %T>MIC for Bb and Mh achieve the breakpoints for these indices10. For Pm the %T>MIC exceeded 70%. Considering these results the authors conclude that DOX at 10 mg/kg daily should ensure the plasma concentrations required for successful therapy against Bb and Mh and possibly against Pm but probably not against Ap10.

Clinical effectiveness and conclusion

The results from clinical investigations of DOX under field conditions in pigs showed that DOX after oral administration at a dose of 10 mg/kg BW was effective in controlling PRDC. The effect was demonstrated in the reduction of respiratory disease incidents, decrease in lethality and increase in economically significant zootechnical parameters with significant differences between the treated and untreated groups4,11. It can be concluded that HydroDoxx® 500 mg/g Powder for use in drinking water administered to pigs at the recommended rate (10 mg/kg BW) is effective to prevent and treat PRDC.

References

Comparative study on the clinical efficacy of Pharmasin® 250 mg/g Premix and Pharmasin® 100% w/w Water Soluble Granules in pigs with experimentally induced respiratory diseases

Stela Vesselova1, Mariana Karanikolova1, Valeri Nazarov1, Valentina Urumova2, Mihni Lyutskanov2, Marin Aleksandrov3, Spas Petkov4, Alain Kanora4

1. Department of R&D, Biovet JSC, Peshtera, Bulgaria; 2. Department of Veterinary Microbiology, Infectious and Parasitic Diseases, Faculty of Veterinary Medicine, Stara Zagora, Bulgaria; 3. Institute of Experimental Pathology and Parasitology, Bulgarian Scientific Academy, Sofia, Bulgaria; 4. Huvepharma NV, Antwerp, Belgium

Introduction

The study objective was to determine the clinical efficacy of orally administered tylosin tartrate in growing pigs that have been artificially infected with Mycoplasma hyopneumoniae (Mh), compared to tylosin phosphate.

Materials and Methods

Four groups of 6 SPF pigs (Danube white), equal number of sexes (10.0–12.0 kg), 10 weeks of age, were used. All groups (I, II and III) were infected with Mh. Twenty-four hours after the challenge, the infected group (I) was treated via feed with tylosin (as phosphate) (Pharmasin® 250 mg/g Premix) and group II was treated through drinking water with tylosin (as tartrate) (Pharmasin® 100% w/w WSG). Both groups received a dose of 10 mg tylosin per kg BW for 8 consecutive days, followed by 5 mg tylosin per kg BW until the end of the period of risk (14 days). The efficacy of the medication was assessed by observing the rectal temperature, clinical symptoms and gross lung lesions, histology, serology for detection of antibodies against Mh using an ELISA test (Dako Cytomation, Denmark A/S), nasal swabs and lung biopsy for bacteriological examinations (after euthanasia and necropsy of all pigs), bodyweight gain and feed conversion efficiency. The results of the examination were determined according to t-test of Student–Fisher.

Results

Specific clinical symptoms of respiratory disease and gross lung and histological lesions were observed in the infected unmedicated group (III). Tylosin (as phosphate) administration via feed in pigs of group I and tylosin (as tartrate) administration via water in pigs of group II both lead to a statistically significant decrease in clinical signs and gross lung lesions (Table 1). Bacteriological examinations of nasal swabs and lung showed a statistically significant reduction in re-isolation rate of Mh (Table 1).

In both tylosin treatment groups, zootechnical parameters (bodyweight gain and feed conversion ratio) were statistically significantly higher than those recorded in the infected unmedicated group of pigs (Table 2).

Table 1. Clinical signs

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of animals with clinical signs</th>
<th>Total clinical scores</th>
<th>No. of animals with lung lesion / total number</th>
<th>Lung lesion scores</th>
<th>Re-isolation from nasal swabs of Mh</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 / 6</td>
<td>10a</td>
<td>1 / 6</td>
<td>2a</td>
<td>1 / 12a</td>
</tr>
<tr>
<td>II</td>
<td>1 / 6</td>
<td>9a</td>
<td>1 / 6</td>
<td>3a</td>
<td>2 / 12a</td>
</tr>
<tr>
<td>III</td>
<td>5 / 6</td>
<td>52b</td>
<td>5 / 6</td>
<td>21b</td>
<td>7 / 12b</td>
</tr>
<tr>
<td>IV</td>
<td>0 / 6</td>
<td>0b</td>
<td>0 / 6</td>
<td>0b</td>
<td>0 / 12a</td>
</tr>
</tbody>
</table>

* p ≤ 0.05

Discussion and Conclusion

Tylosin is one of the oldest antibiotics for veterinary medicine that is still frequently being used to treat enzootic pneumonia. The results show that tylosin (as phosphate) administration via feed and tylosin (as tartrate) administration via water both have a significant metaphylactic and therapeutic effect in experimentally challenged Mh infection in pigs. This is further confirmed by the differences in clinical, bacteriological and zootechnical parameters which were also significantly different compared to group III. The data obtained in this experiment are consistent with the results recorded in previous studies. The significant clinical efficacy of tylosin after oral treatment is due to the wide distribution of the drug in pigs and its reaching and accumulation in target tissues. These results indicate that the use of tylosin administered as tartrate or phosphate can be successfully used in strategic programs to control enzootic pneumonia caused by Mh in pigs.

References

Efficacy of Denagard(tiamulin) and amoxycillin combination on porcine mycoplasmosis control in a Thai pig farm

Mongkol Lumyai¹ Sittikorn Traiyarach¹ Metta Makhanon² Sasiwimon Talummuk² Komkrich Teankum¹ Roongroje Thanawongnuwech¹
1. Chulalongkorn University, Bangkok, Thailand; 2. Novartis (Thailand) Ltd, Bangkok, Thailand

Introduction
Mycoplasmosis is one of major bacterial pneumonia in pigs, usually co-infected with other organisms leading to a complex of respiratory diseases or porcine respiratory disease complex (PRDC)¹. Vaccination is a common tool for controlling the disease; however, the elimination of mycoplasma is still incomplete due to the nature of the organism. By administration of tiamulin (Denagard®), an effective pleuromutilin against mycoplasma², the infection could be significantly resolved. Additionally, a combination of tiamulin with other antibiotics such as amoxycillin could facilitate the elimination of Mycoplasma hyopneumoniae and other concurrent pathogens. The objective of this study was to evaluate the efficacy of a combination of Denagard® and amoxycillin to control concurrent porcine mycoplasmosis in comparison with lincomycin combined with amoxycillin in a Thai pig farm.

Materials and Methods
A mycoplasmosis-affected pig farm in Thailand was selected based on clinical signs, bacterial culture results, slaughter check and serological profile. Serologically, pigs were 100% sero-positive on Mycoplasma indirect ELISA test as early as 16 week-old. Evidently, PRRSV and PCV2 were also detected in this herd. A total of 180 pigs (10 week old) were allocated into 2 groups: Group A (n = 90) fed with Denagard® (100 ppm) and amoxicillin (300ppm) and Group B (n = 90) fed with lincomycin (110ppm) and amoxicillin (300ppm). Those pigs were randomly put into each pen in the same housing without the environmental effect. Treatment was conducted in the growing pig feed from 10 to 14 week-old continuously (one week before the presence of the clinical signs). The clinical history and the production parameters were recorded during the study as well as the number of culled pigs until two weeks after the treatment. To measure average daily weigh grain (ADG) pigs were individually weighted each week from 10 and 14 weeks of age.

Results and Discussion
A higher number of clinically sick and culled pigs were observed in Group B (sick =19, culled pigs =3) than in Group A (sick =11, culled pigs =1) during the studied period (10-14 week-old). Similarly, ADG of Group A pigs receiving a combination of Denagard® and amoxycillin was significantly better than in Group B using Mann Whitney test (P<0.01) (Fig. 1). Concurrent infection among PRRSV, PCV2, Mycoplasma and possibly other bacteria did exist in the studied farm. Interestingly, vaccination of those mentioned 3 major respiratory pathogens was not practised and the combination of Denagard® and amoxycillin did demonstrate helping those treated pigs growing better than the other medicated group. Minimizing the negative effects of secondary bacterial infection using the drugs of choice in this farm is considered as an important management tool to effectively control PRDC. Unfortunately, the lung scores and other lab results were not available at the time of submission.

Acknowledgements
This study was funded by the Novartis Animal Health Inc., Basel, Switzerland.

References
Homogeneity of an oxytetracycline solution administered with a dosing pump

Anne Hemonic; Isabelle Corrègé; Nicolas Berthelot

IFIP-Institut du porc, LeRheu, France

Introduction

On pig farms, collective treatments can be achieved by oral administration of medicines through drinking water with dosing pumps. Homogeneity of the medicated solution at the drinkers is a key factor for therapeutic success, respect of the maximum residue limits (MRL) in meat and prevention of antimicrobial resistance. The aim of this study was to assess homogeneity of an oxytetracycline (OTC) solution, according to type of stock solution tanks and to solubility of OTC.

Materials and Methods

Homogeneity in the stock solution tank

Three types of tanks commonly used on farms (1) were tested:
- One flat-bottomed tank without stirrer,
- One flat-bottomed tank with a motorized propeller,
- One conic-bottomed tank with a pump mixing the solution.

Each tank was filled up with a well-dissolved OTC solution. Sixty samples were taken 3, 5, 7 and 24 hours after the solution had been prepared at 3 heights of the tank (top, middle and bottom).

Homogeneity at the drinker

Tests were conducted on an experimental pipe, simulating on-farm conditions. An OTC solution prepared in a mixing tank with (solution A) or without solvent (solution B) was administered by a hydraulic pump to the drinkers. Fifty or 60 samples of 50 ml were taken at the drinker continuously or after a break, with 4 combinations of water flows and pressures.

Concentrations of OTC were assessed by colorimetric analysis.

Results and Discussion

Homogeneity in the stock solution tank

For the 3 tanks and at a given time, all the coefficients of variation (CV) in the 3 heights and in the entire tank were below 5%. We concluded there was no concentration gradient in tanks at any given time, with or without a stirrer. These results completed those obtained during a test comparing the homogeneity of low or highly soluble preparations of amoxicillin (2).

Homogeneity at the drinker

With solution B, samples taken after each break showed increases and drops of concentrations (figure 1), certainly matching settling and releasing of OTC in the pipe. This didn’t occur with continuous sampling but in both cases, CV were up to 5% for the 4 combinations of flows and pressures (Figure 1). So, without any solvent, the solution wasn’t homogeneous at the drinker.

With continuous sampling of solution A, CV were below 5% and average concentrations were between 104 and 109% of the expected concentration (1g/l) (Table 1). This met the quality requirements of an industrial medicated feed.

After a 12 hour break of solution A, the first samples showed concentration levels between 1.2 and 2.5 times higher than the average levels of the next samples. The involved volume (400 ml), corresponding to the pipe coming down towards the drinker, might globally match the first morning-time drinking of one pig weighting 70 kg (less than 6% of its daily water intake). So, this doesn’t question the respect of the MRL.

Conclusion

Our results demonstrate that a well-dissolved medicated solution guarantees a correct homogeneity in the stock solution tank even without a stirrer. At the drinker, the homogeneity of such a solution meets the quality requirements of an industrial medicated feed.

References

**Stability of different amoxicillin medicated premixes in flour feed**

Eric Bousquet1 Mehdi Laraichi1 Guillermo Cano2 Aurélien Guicherd3 Jacques Goutaliere3

1. Virbac, Carros, France; 2. Tests and Trials, Lleida, Spain; 3. Phatophy, Lyon, France

**Introduction**

Interest of a specific coating process of amoxicillin (Suramox®) has been previously demonstrated in order to protect active ingredient degradation in medicated feeds and to insure that adequate amount of active ingredient is available for pigs (1-2). Different comparative studies at laboratory, pilot or industrial scale in Europe showed a better protection of amoxicillin with this coating process against degradation during pelletization and storage of feeds (3).

As medicated feeds are also used in some countries as flour feeds (without pelletization), objective of the present study was to compare stability of amoxicillin in flour feed at industrial scale for different medicated premixes registered in Europe.

**Materials and Methods**

Five products containing respectively 5% (Suramox®, A, B, C) and 10% (D) of amoxicillin (expressed as base) were tested in the same Spanish feed plant. One batch of a pig grower feed was supplemented by each premix at the concentration of 400 ppm (mg of amoxicillin per kg feed). One blank feed batch was manufactured between 2 medicated batches to avoid cross contamination. Size of medicated feed batches was equal to 3 tons each. Mixing of raw materials lasted for 2.5 minutes in the mixer where each premix was added manually. Amount of each premix was accurately weighed in order to calculate exact concentration of amoxicillin in feed. Three samples of each medicated feed batch were taken at regular intervals covering the total emptying time of the mixer and stored during 14 days in standardized conditions (respectively 30°C/65% of relative humidity (RH) and 40°C/75% RH before assay). Amoxicillin concentrations in feed were determined by High Performance Liquid Chromatography with UV detection. Each sample was analyzed twice and mean concentration was calculated.

**Results**

Lower degradation rates were measured with Suramox® (6.1% and 13.9% after storage at 30°C and 40°C respectively) than with the other products (degradation ranging from 30.5% to 44.4% and from 45.2% to 60.3% after storage at 30°C and 40°C respectively).

**Table:** Amoxicillin mean concentrations in feed after storage during 14 days (expressed as percentage of theoretical concentration)

<table>
<thead>
<tr>
<th>Product</th>
<th>Storage at 30°C</th>
<th>Storage at 40°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suramox</td>
<td>93.9%</td>
<td>86.1%</td>
</tr>
<tr>
<td>A</td>
<td>69.5%</td>
<td>54.8%</td>
</tr>
<tr>
<td>B</td>
<td>60.4%</td>
<td>50.9%</td>
</tr>
<tr>
<td>C</td>
<td>55.6%</td>
<td>42.5%</td>
</tr>
<tr>
<td>D</td>
<td>61.4%</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

**Discussion**

Degradation during storage has been previously shown at laboratory scale when flour feed was stored during 15 days at 40°C/95% RH: degradation was limited to 10% for Suramox® and around 50% for other products, consistent with present data (3).

This study confirms that amoxicillin may be damaged in feed even without pelletization during transport and storage according to temperature and humidity conditions found in Europe (particularly when feed is stored in silos during summer). A specific coating process of the active ingredient may reduce degradation in such conditions.

**References**

Stability of tylosin in liquid feed used in commercial pig farms

Alain Kanora; Spas Petkov; Koen De Gussem
Huvepharma NV, Antwerp, Belgium

Introduction
In some countries, pig farms are using recyclable foodstuff originating from human consumption and are commonly being added as nutritional basis for liquid feeds. Farmers can also mix commercial feed with water to obtain liquid feed. These two feed systems have the benefit that feed becomes tastier and more acid due to fermentation; both properties will increase consumption. The stability and activity of veterinary medicinal products (VMP) used in liquid feed are often not studied; particularly data on antibiotics are unavailable.

VMD (UK) currently allows the use of in-feed antimicrobials in liquid feed in accordance with the cascade regulations, but veterinarians need to base their decision on the stability of the veterinary specialty first before prescribing the use in liquid feed. In this way issues like overdosing, underdosing, resistance build-up, etc. can be avoided. Therefore, the use of tylosin phosphate (Pharmasin® medicated feed premix) in liquid feed was studied by evaluating the impact on the active substance with regards to stability.

Materials and Methods
Locally collected dry feed from a GMP certified production site was sourced and diluted at ration 2:1 with tap water to obtain a liquid feed matrix.

Pharmasin® 250 mg/g and Pharmasin® 100 mg/g were added to the liquid feed in dosages providing 100 ppm in the feed based on dry matter.

The mixtures were stored under normal environmental conditions (20-25°C, ambient humidity) and sampled at 0, 1, 6, 24 and 72 hours.

The samples were analyzed by a microbiologic assay for tylosin content. The method is a four-dose diffusion assay using Micrococcus luteus ATCC 9341 as a test micro-organism.

Results
The ppm levels of all tested Pharmasin® formulations remained perfectly stable for more than 5 hours. The VMD recommendation of 1h stability was perfectly matched and also the maximum meal contact time for pigs was prior to onset of a slight activity loss.

<table>
<thead>
<tr>
<th>Product</th>
<th>0</th>
<th>1</th>
<th>6</th>
<th>24</th>
<th>72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmasin® 250</td>
<td>115</td>
<td>114</td>
<td>111</td>
<td>102</td>
<td>94</td>
</tr>
<tr>
<td>Pharmasin® 100</td>
<td>114</td>
<td>111</td>
<td>112</td>
<td>101</td>
<td>96</td>
</tr>
</tbody>
</table>

Discussion and Conclusion
It can be concluded from this study that Pharmasin® Medicated Premix used in a responsible way in liquid feed remains perfectly stable and that there is no loss of activity of the used tylosin phosphate. Even after 24 and 72 hours, tylosin activity was in excess of 80% of the initial value.

References
**Pharmacokinetics and tolerance of Catosal® in pigs**

**Bernard H. Schmidt¹ Ralph Krebber² Martina Rehagen¹**

¹. Bayer Animal Health GmbH, Leverkusen, Germany; ². Bayer CropScience AG, Monheim, Germany

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**Introduction**

Catosal® is a metabolic stimulant for use in numerous target animal species including the pig in many countries worldwide. It contains 100 mg of butafosfan and 0.05 mg of cyanocobalamin (vitamin B12) per ml. Experimental studies indicated that Catosal® attenuates stress responses of piglets (1), and reduces the prevalence of certain production diseases in sows and piglets (2,3). The present report documents the tolerance and the pharmacokinetics of butafosfan after a single intramuscular (i.m.) injection of Catosal® to piglets.

**Materials and Methods**

Two independent studies were performed in an accredited experimental animal centre in Germany. The first one assessed the local and systemic tolerance of Catosal® in healthy German Landrace hybrid piglets (22.5 – 28.5 kg body weight (b.w.)). Catosal® was injected i.m. at the dosages of 0.1, 0.3, and 0.5 ml/kg (N=6 per dose group). A control group of 6 piglets received saline at the dose volume of 0.5 ml/kg b.w. Between injection and the third day thereafter, the animals were closely monitored for clinical signs of intolerance and local reactions at the injection site.

The second study assessed the pharmacokinetics of butafosfan in four Hamshire/Pietrain piglets weighing 36.5 – 47.0 kg. The animals received Catosal® at a dose volume of 0.1 ml/kg i.m., corresponding to 10 mg butafosfan/kg b.w. Frequent blood sampling was performed over a period of 24 hours after treatment. Serum was analyzed for butafosfan concentrations using HPLC with tandem mass spectrometric detection. Relevant pharmacokinetic parameters were calculated using non-compartmental analysis and the linear/log trapezoidal rule. All results are given as arithmetic means ± standard deviation.

**Results**

Tolerance: No local reactions at the injection site, immediate systemic reactions or other adverse events were observed in either study after i.m. injection.

Pharmacokinetics: Based on the individual serum concentrations of butafosfan, the concentration-time profiles depicted in Figure 1 were obtained.

**Figure 1** Individual butafosfan concentration-time profiles of pigs injected intramuscularly with Catosal® (0.1 ml/kg)

Group mean maximal concentrations of 35 ± 5.8 μg/L were measured 0.3 ± 0.1 hrs after administration. The elimination half life time was calculated to 3.5 ± 0.6 hrs. Within 24 hours post-administration, serum butafosfan levels approached the limit of quantitation of 0.02 mg/L. The area under the curve extrapolated ad infinitum was 72.5 ± 12.6 hr*μg/L. The distribution volume and clearance of the absorbed fraction were 775 ± 150 L/kg and 148 ± 20.6 L/hr/kg, respectively. The mean residence time extrapolated ad infinitum was 2.7 ± 1.0 hrs.

**Conclusion**

Intramuscular injection with Catosal® at a dose volume of 0.1 ml/kg b.w. and 5 times thereof is well tolerated and safe in pigs. The pharmacokinetics of butafosfan show a fast and efficient absorption into blood, a high distribution volume and fairly rapid elimination from the porcine body.

**References**

Stability of different amoxicillin medicated premixes in pelleted feed

Eric Bousquet1 Mehdi Laraichi1 Guillermo Cano2 Aurélien Guicherd3 Jacques Goutalier3
1. Virbac, Carros, France; 2. Tests and Trials, Lleida, Spain; 3. Phatophy, Lyon, France

Introduction

Interest of a specific coating process of amoxicillin (Suramox®) has been previously demonstrated in order to protect active ingredient degradation in medicated feeds and to insure that adequate amount of active ingredient is available for pigs (1-2). Different comparative studies at laboratory, pilot or industrial scale in Europe showed a better protection of amoxicillin with this coating process against degradation during pelletization and storage of feeds (3-4).

Objective of the present study was to complete stability data of amoxicillin in pelleted feed at industrial scale for different medicated premixes registered in Europe.

Materials and Methods

Five products containing respectively 5% (Suramox®, A, B, C) and 10% (D) of amoxicillin (expressed as base) were tested in the same Spanish feed plant. One batch of a pig grower feed was supplemented by each premix at the concentration of 400 ppm (mg of amoxicillin per kg feed). One blank feed batch was manufactured between 2 medicated batches to avoid cross contamination. Size of medicated feed batches was equal to 3 tons each. Amount of each premix was accurately weighed in order to calculate exact concentration of amoxicillin in feed. Steam pressure was equal to 4 atm and temperature ranged from 53.7 to 65.5°C before pelletization. Temperature ranged from 71.3 to 75.2°C after pelletization. Six samples of each medicated feed batch were taken after cooling of the pellets at regular intervals covering the total batch delivery. Samples were analyzed at the time T0 of reception by the laboratory (Phatophy). In the meantime, aliquots of 3 out of 6 samples per batch were stored during 14 days in standardized conditions (25°C/65% of relative humidity (RH) before assay at T14). Amoxicillin concentrations in feed were determined by High Performance Liquid Chromatography with UV detection. Each sample was analyzed twice and mean concentration was calculated.

Results

Mean degradation ranged from 10.2% to 39.3% at T0. A further degradation was measured during storage for all products except Suramox®, leading to a total degradation between 18.3% and 53.1% at T14 for products A, B, C and D.

Table Amoxicillin mean concentrations in feed at T0 and after storage during 14 days (expressed as percentage of theoretical concentration)

<table>
<thead>
<tr>
<th>Product</th>
<th>T0 (n=6)</th>
<th>T14 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suramox</td>
<td>89.8%</td>
<td>91.2%</td>
</tr>
<tr>
<td>A</td>
<td>87.6%</td>
<td>81.7%</td>
</tr>
<tr>
<td>B</td>
<td>75.6%</td>
<td>64%</td>
</tr>
<tr>
<td>C</td>
<td>60.7%</td>
<td>46.9%</td>
</tr>
<tr>
<td>D</td>
<td>68.7%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Discussion

Degradation was limited around 10% for Suramox®, without significant evolution during storage (variation within analytical variability). Degradation recorded for the other products was consistent with previous studies following pelletization and eventual storage of pig medicated feeds (3-4).

This study confirms that a specific coating process of the active ingredient may reduce degradation after pelletization and storage of feeds.

References

**Demixing by elutriation of different amoxicillin medicated premixes in feed**

Eric Bousquet1 Mehdi Laraichi1 Carine Rousseau1 Christine Segot1 Aurélien Guicherd2 Jacques Goutalier2

1. Virbac, Carros, France; 2. Phatophy, Lyon, France

**Introduction**

Demixing of medicated feeds is a concern for feed millers and veterinary practitioners, leading to heterogeneous feeds and increase of antimicrobials dosage variability. Elutriation is a demixing phenomenon due to different speeds of powder particles while falling through the air. A standardized test has been developed to assess elutriation of powders from previously described experiments (1). This test has been correlated with demixing of supplemented feeds in plants (2) and previously performed for a range of antimicrobials premixes (3-4). Objective of this study was to complete elutriation tests on 4 amoxicillin premixes registered in Europe.

**Materials and Methods**

Four products containing respectively 5% (Suramox®, A) and 10% (B, C) of amoxicillin (expressed as base) were tested in a pre-starter feed (median particle size : 390 μm ). Median particle size of the 4 products was determined by laser granulometry. Each product was then tested twice in order to allow statistical analysis. Around 1 kg of flour feed was supplemented by each product according to incorporation rate recommended (400 ppm of amoxicillin in feed). A tracer was added in each feed sample at the concentration of 500 ppm in order to validate the tests. For each test a 300 ml feed sample was dropped in an 8 m high tube. After drop, top and bottom 50 ml feed samples were taken for tracer assay by colorimetry and amoxicillin assay by high performance liquid chromatography. In each test, an elutriation index (EI) was calculated from previously defined index for the tracer and for amoxicillin (where Ct and Cb are respectively concentrations in top and bottom samples):

\[ EI = \frac{Ct - Cb}{Ct + Cb} \times 100 \]

This index ranges from −200 to +200, extreme values corresponding to maximal demixing whereas zero value corresponds to lack of demixing. A non parametrical analysis of variance on ranks was performed to compare EI between products.

**Results**

Amoxicillin EI was lower for Suramox® than for the other products.

<table>
<thead>
<tr>
<th>Product</th>
<th>Particle size (μm)</th>
<th>EI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suramox</td>
<td>380</td>
<td>1.4</td>
</tr>
<tr>
<td>A</td>
<td>878</td>
<td>-89.4*</td>
</tr>
<tr>
<td>B</td>
<td>902</td>
<td>-137.2*</td>
</tr>
<tr>
<td>C</td>
<td>188</td>
<td>95.1*</td>
</tr>
</tbody>
</table>

*, **: significantly different from Suramox® (resp p<0.05 and p<0.005)

**Discussion**

For products with high negative EI, amoxicillin is more concentrated in bottom of the sample after test (amoxicillin particles too large or too dense falling more quickly within large feed particles). For products with high positive EI, amoxicillin is more concentrated in top of the sample after test (thin amoxicillin particles falling more slowly within thin feed particles). This is reflected by median particle size higher than feed one for products with high negative EI (products A and B) and median particle size lower than feed one for product with high positive EI (product C). Lower demixing with Suramox® may be due to amoxicillin particle size with specific coating process (median particle size : 380 μm), consistent with feed median particle size (390 μm).

**Acknowledgements**

The authors thank Fabrice Putier and Marianne Jousselin from Tecaliman (France) for performance of elutriation tests.

**References**

Introduction
A synergistic effect has been demonstrated when Denagard® (tiamulin) and chlortetracycline (DEN-CTC) are used concurrently in-feed to address the effects of bacterial pneumonia.1 The economic benefit of administering DEN-CTC in-feed has been documented by others.2, 3 The purpose of this study was to evaluate the performance differences in disease control between pigs fed no in-feed antibiotic, OTC (oxytetracycline 440 ppm) or DEN-CTC (38.5 ppm tiamulin; 440 ppm chlortetracycline).

Materials and Methods
A total of 1344 weaned pigs (avg. age 21 days) were placed in one of two all-in all-out commercial wean to finish barns. Pigs were fed common diets throughout the nursery phase (D1(weaning)-D39). On day 39, pigs were mixed by gender and allocated to one of three treatment groups (3 x 2 factorial design): no medication, OTC or DEN-CTC. The in-feed antibiotic was fed for 17 days followed by a subsequent 17 days of no medication (total trial D39-D73). Data analysis for average daily gain (ADG) and feed efficiency (F:G) were done using all weight in, all weight out and total feed consumed. Pen averages were used as the experimental unit with 16 pens/treatment.

Results
The DEN-CTC group had an ADG advantage over the non-medicated (0.07 kg/day) and the OTC (0.05 kg/day) groups for the entire 34 day trial (p < 0.001; Table 1). This resulted in the DEN-CTC pigs being significantly heavier than the non-medicated (2.59 kg) or OTC pigs (1.77 kg) at the end of the 34 day trial (p < 0.001) period. The DEN-CTC group showed an improved F:G compared to the non-medicated or the OTC group (p < 0.09). This resulted in the DEN-CTC pigs requiring 2.54 kg and 2.81 kg less feed to reach the same end weight as the non-medicated or OTC pigs, respectively. The in-feed antibiotic increases costs by $0.12 USD per head for the OTC pigs and, $0.61 USD per head for the DEN-CTC pigs. If one assumes a $140 USD per ton feed cost and a market price of $40 USD per hundred pounds, the DEN-CTC treatment returned $2.67 USD more per head than the non-medicated and $1.99 USD more per head than the OTC treatment. Each Dollar spent on Denagard plus chlortetracycline returned $ 4 USD in improved performance over no medication or oxytetracycline in-feed medication.

Discussion
In the investigated production system the impact of Denagard plus chlortetracycline early in the grow finish phase had a significant impact in improving performance during and after the in feed antibiotic application. The improvements in performance translate into improved return on investment for the production system of $4 USD per head over either the non medicated or OTC treatments.

References

Table 1. Performance Effect by in feed antibiotic (D39-D73) application Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Med</th>
<th>OTC</th>
<th>DEN-CTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start weight (D39)</td>
<td>25.92</td>
<td>25.97</td>
<td>25.92</td>
</tr>
<tr>
<td>ADG</td>
<td>0.75ab</td>
<td>0.77b</td>
<td>0.82b</td>
</tr>
<tr>
<td>F:G</td>
<td>2.05a</td>
<td>2.06a</td>
<td>1.96b</td>
</tr>
<tr>
<td>End Weight (D37)</td>
<td>51.62a</td>
<td>52.44a</td>
<td>54.21b</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>0.70</td>
<td>0.70</td>
<td>0.90</td>
</tr>
</tbody>
</table>

different superscripts by row are statistically significant at p< 0.05
Monitoring of antimicrobial usage for pigs in Denmark

Helle Stege1 Claes Enoe2 Erik Jacobsen2 Lis Alban3 Jens P. Nielsen1

1. KU-Life, Copenhagen, Denmark; 2. Vetinst, Copenhagen, Denmark; 3. VSP, Kjellerup, Denmark

Introduction
The Danish system for monitoring of veterinary drug use, Vetstat, was implemented during 1999 - 2001 (1). Close to 100% of the drugs used in pig herds are provided on prescription, hence, reported to Vetstat from pharmacies. The aim of this presentation was to present the antimicrobial (AM) usage for pigs during 2004-2009.

Materials and Methods
The overall use of AM in Denmark (measured as kilo active compound) was downloaded from the Vetstat homepage. In general pigs account for 80% of the total usage of AM. The number of slaughter pigs produced per year (including export of live growers of 30 kg) was obtained from Danish Statistics. When Vetstat data from 2009 were extracted they only included entries until September so the total use of this year was estimated by extrapolation (table 1). When comparing the AM use between farms and/or veterinarians, the total amount of active compound must be converted to “number of Animal Defined Daily Doses, ADD” (2), according to the products’ potency and concentration and the animal’s weight. The measure used to compare AM usage between farms/ veterinarians is “percentage animals treated per day” which is calculated as: Average number of ADDs used per day divided by the average number of animals present. ADD data on AM usage for pigs were extracted from Vetstat (User page).

Results
Overall AM usage (kg) in Denmark, 2004-2009 is presented in fig. 1 and table 1. Apart from the increase from 2008 to 2009 (t-test; p = 0.02) there has been no significant changes in the average AM usage (g/pig/year) during the years. The most-used-AMs for pigs were tetracyclines, penicillins, sulpha-tmps, macrolides and tiamulines. The main part of the AM was prescribed for per oral administration to growers for gastro-intestinal disorders. Based on ADD calculations, the present national average is 10-12% growers treated per day as opposed to 1.5-2% for breeding stock and 2% for finishers (data from Vetstat, User page, not presented).

Discussion
The overall AM usage is reported from the pharmacies (>95%) by automated transfer to Vetstat, based on their stock managing system. The conversion from actual prescription to amount of active compound is formalized and simple. Hence, these data are very reliable. The AM usage has been stable during 2004-2009 with an average use of 3.5 - 4.0 g AM per produced slaughter pig per year (table 1). Similarly, the usage measured as ADDs or percentage animals treated per day have been reasonably stable during the years. However, ADD data are more prone to errors because of the assumptions and calculations involved.

Table 1. Overall use of AM (kg) per year - mean and stddev. Pigs account for 80% of total use. AM use per pig (g/pig/year) is presented. The apparent increase in AM/pig/year was tested (t-test) comparing 2007 with 2009 and 2008 with 2009, respectively.

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>113,897</td>
<td>114,173</td>
<td>116,475</td>
<td>122,438</td>
<td>121,435</td>
<td>131,132</td>
</tr>
<tr>
<td>Mean</td>
<td>9.49</td>
<td>9.51</td>
<td>9.71</td>
<td>10.2</td>
<td>10.12</td>
<td>10.93</td>
</tr>
<tr>
<td>Stddev</td>
<td>506.4</td>
<td>582.8</td>
<td>769.3</td>
<td>976.2</td>
<td>747.6</td>
<td>682.2</td>
</tr>
<tr>
<td>Pigs/year</td>
<td>24.9</td>
<td>25.8</td>
<td>25.7</td>
<td>26.3</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>G/pig/year</td>
<td>4.57</td>
<td>4.43</td>
<td>4.53</td>
<td>4.66</td>
<td>4.67</td>
<td>5.04</td>
</tr>
<tr>
<td>(x 80%)</td>
<td>3.66</td>
<td>3.54</td>
<td>3.63</td>
<td>3.72</td>
<td>3.74</td>
<td>4.03</td>
</tr>
</tbody>
</table>

References
Assessment of exposure of Draxxin® compared to Draxxin plus iron administered to 3 day old piglets

Steven P. Lesman1, Ian A. Nanjiani2, James R. Allison3, Ann E. Fielder1, Clark D. Smothers1, Scott A. Brown1, Joseph A. Robinson1


Introduction

Although undesirable from a pharmaceutical perspective, and usually off-label in terms of product directions, it is common farm practice in some countries for injectable products to be mixed immediately prior to administration. The advantage of this procedure is that it minimizes the number of injections that have to be given to animals. The downside is that it creates the possibility of interactions that could affect drug safety and/or efficacy, both in the form of pharmacological interactions between the active ingredients and chemical reactions between the formulations. The latter are most likely to affect absorption kinetics from the site of injection and influence drug bioavailability.

Iron injections are commonly given to piglets in the first week of life to counteract the low iron content of the sows' milk. Draxxin® (Pfizer Animal Health) is an injectable formulation of the antibiotic tulathromycin that is sometimes given to piglets of the same age. There have been reports of producers mixing the products prior to injection. Although Draxxin is considered a long-acting product, the duration of activity derives from the intrinsically long half-life of tulathromycin, which accumulates in lung tissue and establishes therapeutic concentrations that persist for many days. The formulation is an aqueous solution that allows rapid absorption of drug from the site of injection. The greatest pharmaceutical risk, therefore, is of an incompatibility that delays or prevents drug uptake and reduces bioavailability. This study was performed to investigate this possibility. Based on previous pharmacokinetic work, lung concentrations of tulathromycin at 24 hours were used to assess the overall outcome of the drug absorption phase.

Materials and Methods

This two-treatment randomized parallel group study was designed to compare Draxxin (tulathromycin) mixed with iron to Draxxin alone when dosed intramuscularly to 3-day old Landrace/Duroc cross piglets. The doses were Draxxin 2.5 mg/kg bodyweight and 200 mg iron (Ursoferran®)/animal. Sixteen piglets were randomized to each treatment group according to a generalized block design. Blocking was based on litter and pen location. At 24 hr, blood was collected for PK and necropsies performed to harvest lung tissue. The plasma and lung homogenate samples were analyzed for tulathromycin concentrations by an LC-MS/MS procedure.

Results

The concentration data are summarized in the following table:

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Treatment†</th>
<th>Least Squares Mean</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (ng/mL)</td>
<td>T01</td>
<td>37.8</td>
<td>22.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Plasma (ng/mL)</td>
<td>T02</td>
<td>35.4</td>
<td>21.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Lung (ng/g)</td>
<td>T01</td>
<td>3270</td>
<td>2990</td>
<td>3570</td>
</tr>
<tr>
<td>Lung (ng/g)</td>
<td>T02</td>
<td>3290</td>
<td>3010</td>
<td>3600</td>
</tr>
</tbody>
</table>

†T01: Draxxin alone T02: Draxxin + Iron

Non-inferiority was demonstrated comparing Draxxin with iron (T02) to Draxxin alone (T01). The 95% confidence intervals for the ratios of Draxxin with iron to Draxxin alone were 83 - 106% and 92 - 110% for tulathromycin concentrations in plasma and lung homogenate, respectively.

Discussion

Both plasma and lung tissue concentration data show that T02 (Draxxin administered with iron) was not inferior to T01 (Draxxin alone). This study demonstrated that the mixing of Draxxin with a commonly used commercial injectable iron solution did not adversely affect the lung and plasma tulathromycin concentrations at 24 hours post injection in 3 day old, commercially reared pigs. The study did not specifically address safety, but no adverse events were noted. Unapproved mixing of products is to be discouraged, but this study did not reveal any specific adverse impact.

Reference

**In vitro activity of Florfenicol with other antimicrobials**

Timothy S. Kniffen¹ Elliot Stevens² Darin Madson³

1. Intervet/Schering-Plough Animal Health, DeSoto, KS, USA; 2. Rural Technologies, Inc., Brookings, SD, USA; 3. Iowa State University, Ames, IA, USA

**Introduction**

Florfenicol is a broad spectrum antimicrobial approved for use in swine in most pig producing countries. It is approved for use variably as a premix, drinking water concentrate, and/or injectable formulation. Florfenicol is primarily used in swine for the treatment and prevention of respiratory disease. There is no guidance currently available to swine veterinarians concerning the use of florfenicol sequentially with other antimicrobials. A checkerboard dilution technique was utilized to assess the activity of florfenicol with antimicrobial combinations against 4 bacterial pathogens of swine. The results of this checkerboard evaluation provide the first available guidance to swine veterinarians utilizing florfenicol sequentially with other antimicrobials.

**Materials and Methods**

**Bacterial Isolates:**

Four bacterial isolates were used in this pilot project: *Streptococcus suis* (Ss), *Salmonella choleraesuis* (Sc), and *Bordetella bronchiseptica* (Bb). *Escherichia coli* (Ec) was also included although it is not one of the respiratory pathogens for which florfenicol has been approved. All bacterial isolates were obtained from swine field cases submitted to a diagnostic laboratory.

**Antimicrobials Evaluated:**

Antimicrobial concentrations were tested with florfenicol as serial dilutions in the ranges indicated in Table 1.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Antimicrobial</th>
<th>Dilution Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ffc</td>
<td>florfenicol</td>
<td>0.25-8 µg/ml</td>
</tr>
<tr>
<td>Ce</td>
<td>ceftiofur</td>
<td>0.12-8 µg/ml</td>
</tr>
<tr>
<td>Ctc</td>
<td>chlorotetacycline</td>
<td>0.5-8 µg/ml</td>
</tr>
<tr>
<td>En</td>
<td>enrofloxacin</td>
<td>0.12-2 µg/ml</td>
</tr>
<tr>
<td>Otc</td>
<td>oxytetracycline</td>
<td>0.5-8 µg/ml</td>
</tr>
<tr>
<td>Tc</td>
<td>tetracycline</td>
<td>4.0-32 µg/ml</td>
</tr>
<tr>
<td>Tm</td>
<td>tiamulin</td>
<td>1.0-32 µg/ml</td>
</tr>
<tr>
<td>Ty</td>
<td>tylosin tartrate</td>
<td>0.5-32 µg/ml</td>
</tr>
<tr>
<td>Tu</td>
<td>tulathromycin</td>
<td>1.0-64 µg/ml</td>
</tr>
</tbody>
</table>

**Bacterial Susceptibility:**

The minimum inhibitory concentration (MIC) of each antimicrobial tested was determined for each of the four bacterial isolates selected. The checkerboard dilution technique was then utilized to allow calculation of the fractional inhibitory concentration index (FICI) for florfenicol in combination with other antimicrobial agents. The combinations were then categorized based on FICI results as synergistic (S), antagonistic (A), or indifferent (I).

**Fractional Inhibitory Concentration Index**

<table>
<thead>
<tr>
<th>Ffc</th>
<th>Ce</th>
<th>Ctc</th>
<th>En</th>
<th>Otc</th>
<th>Tc</th>
<th>Tm</th>
<th>Ty</th>
<th>Tu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ss</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Sc</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
</tr>
<tr>
<td>Ec</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Bb</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>S</td>
</tr>
</tbody>
</table>

**Discussion**

1. Most antimicrobials tested *in vitro* in combination with florfenicol were indifferent in effect.
2. No antagonistic interactions were found between florfenicol and any tested antimicrobial *in vitro*.
3. Synergistic relationships between florfenicol and OTC and between florfenicol and tulathromycin were detected *in vitro*.
4. These *in vitro* results suggest that antimicrobials commonly used in swine medicine would have no anticipated antagonistic effects when used sequentially with florfenicol.

**References**

Monitoring of enrofloxacin (Baytril®) sensitivity of clinical field bacterial strains from pigs in the Benelux using E testing

Dominique Gevaert
Bayer SA-NV, Diegem (Machelen), Belgium

Introduction
In veterinary routine diagnostic laboratories antimicrobial sensitivity testing is performed by agar disc diffusion. The E test (AB Biodisk, Solna, Sweden) is a newer technique offering technical and veterinary advantages, because the result is expressed as the minimal inhibitory concentration (MIC, μg/ml) rather than sensitive, intermediate or resistant. For concentration dependent antibiotics such as fluoroquinolones, AUC/MIC and Cmax/MIC ratios have been described as predictive for the clinical outcome and thus valuable indicators in routine veterinary practice (1). Bayer has established with the leading veterinary routine diagnostic laboratories in the Benelux a protocol to use the E test for enrofloxacin (Baytril®, Bayer) on all bacteria isolated from routine samples against which Baytril is registered in swine.

Material and Methods
Between June 2005 and January 2010, the E test for enrofloxacin was carried out routinely on all swine pathogens, isolated by 4 laboratories in the Benelux and falling under the scope of the various marketing authorisations for Baytril in swine. Samples were submitted by practitioners. A bacterial suspension was spread onto Mueller-Hinton plates and the E test for enrofloxacin was put on its surface. Enrofloxacin concentration ranged from 0.002 up to 32 μg/ml. After overnight incubation at 37°C, the MIC was read where the zone of growth inhibition intersected the MIC scale on the strip. The concentration inhibiting growth of at least 90% (MIC90) of the isolates was calculated.

Results
In total 2339 swine pathogens examined. The MIC90 value and respective number of strains is as follows: Actinobacillus pleuropneumoniae: 0.094 (n=413), Bordetella bronchiseptica: 1 (n=103), Escherichia coli: 1 (n=1116), Pasteurella/Mannheimia spp.: 0.032 (n=475), Salmonella spp.: 0.25 (n=232). A total of 87 isolates with MIC exceeding 2 μg/ml were found (3.7%). No relevant differences in sensitivity of strains between the participating laboratories were found.

Discussion
The E test is not often used for routine bacteriology because of the costs of the test. However, routine monitoring of has proven to be feasible under field conditions. It supports swine veterinarians in their treatment schedule: the lower registered dose of 2.5 mg enrofloxacin per kg bodyweight can still be recommended for infections caused by Actinobacillus pleuropneumoniae and Pasteurella/Mannheimia spp.. The registered higher dose of 5 mg enrofloxacin per kg bodyweight is recommended in infections caused by Bordetella bronchiseptica, Escherichia coli and Salmonella. Even after more than 20 years of use of Baytril in the Benelux, the registered bacteria remain highly sensitive to enrofloxacin. However, this may change upon the introduction of several cheap generics, because generics have shown to lead to increase in use and, subsequently, the rise of resistance (2).

References
Comparison of the efficacy of a florfenicol (Nuflor®) feed premix with an analogous product in the treatment of Swine Respiratory Disease (SRD)

Alberto E. Cevidalli1 Ernesto Bongiovanni2 Marco Bosetti3
1. Intervet Schering-Plough Animal Health, Peschiera Borromeo, Italy; 2. Practitioner, Casalbellotto, Italy; 3. Practitioner, Soncino, Italy

Introduction
Florfenicol is a broad spectrum antibiotic of the phenicol group. Previous studies have shown it to be highly efficacious in the treatment of SRD, when administered intramuscularly (1,2,3,). The object of this comparative field trial was to evaluate the efficacy of florfenicol administered in feed at a dose rate of 10 mg/kg body weight for five consecutive days in the treatment of SRD under Italian field conditions.

Materials and Methods
The trial was carried out on the grower units of two farrow-to-finish herds. If at least 10% of the pigs in a pen exhibited acute respiratory signs, the pen was included in the trial and randomly allocated to one of the following treatments: florfenicol medicated feed 200 ppm (Nuflor premix Intervet Schering-Plough) or a feed containing a combination of two antibiotics (1400 ppm of sulfadimethoxine and 560 ppm of chlortetracycline). Pens were included independently of each other once the inclusion criteria had been met, and the treatment period was 5 days (days 0-4). The experimental unit was the pen and both populations (clinically ill and exposed) were commingled in each pen.

The parameters on which efficacy was assessed included: rectal temperature, dyspnea, depression and Clinical Illness Index Score (CIIS). The animals were observed for 12 days (Day 0 to Day 11). Success rates, i.e. therapeutic success for the 'ill' population, and the prevention of illness for the 'exposed' population, were recorded on Day 6 and on Day 11.

Results
Seven hundred and thirty-three pigs were included in the trial on Day 0: 117 were showing acute respiratory signs and 616 belonged to the exposed population. Altogether, 422 pigs were treated with florfenicol-medicated feed and 311 with the control product.

With the exception of prevention in the exposed animals on Day 6 (when the success rates were equal for both groups), the florfenicol-medicated animals always performed better. With respect to the individual parameters (rectal temperature, dyspnea, depression, CIIS), in general, florfenicol always showed better results, in some particulars with statistical significance.

Table 1. Cumulative success rates of the two trial sites

<table>
<thead>
<tr>
<th>Group</th>
<th>‘Ill’ population</th>
<th>‘Exposed’ population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapeutic</td>
<td>Therapeutic</td>
</tr>
<tr>
<td></td>
<td>success</td>
<td>success</td>
</tr>
<tr>
<td></td>
<td>Day 6</td>
<td>Day 11</td>
</tr>
<tr>
<td>FFC</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>Sulf +</td>
<td>87</td>
<td>73</td>
</tr>
<tr>
<td>CTC</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Discussion
Statistical analysis of the primary end-points (success rates) demonstrated that florfenicol-medicated feed was not inferior to a medicated feed containing high levels of the control product. The analysis of the secondary end-points (clinical parameters) confirms altogether greater efficacy for the florfenicol medication, some of the differences for individual parameters being statistically significant.

In respect of the treatment of ill pigs, the average rectal temperature of the florfenicol-treated group was statistically significantly lower than that of the control group (p<0.05) over the period measured (days 1-5).

References
Effects on overall production of the treatment of piglets with NUFLOR® PREMIX on a farm with respiratory disease

Manolo Toledo1 Rut Menjon2 Jesus M. Bollo2 Marta Jimenez2
1. Piensos Jimenez S.L., Lorca, Murcia, Spain; 2. Intervet Schering Plough, Madrid, Spain

Introduction
The aim of the study was to assess the efficacy of the in-feed treatment of piglets with florfenicol to prevent losses caused by swine respiratory disease, during both treatment and subsequent production phases.

Florfenicol (Nuflor® 40 mg/g Premix for Swine), a new broad-spectrum antimicrobial, is a 3rd generation phenicol, a fluorinated analogue of thiamphenicol obtained by substituting one hydroxyl group with fluorine. A methyl sulfonyl group (CH3-SO2) replaces the p-nitro group (NO2) found in chloramphenicol, thus ruling out the risk of aplastic anemia. This also provides a broader spectrum of activity and prevents the chloramphenicol acetyltransferase (CAT) resistance problems of thiamphenicol and chloramphenicol (2).

Materials and Methods
The trial farm, in a high stock density area of southeast Spain, houses 2,000 sows in three cycles. The farm is positive and unstable for PRRS. Sows are blanket vaccinated four times per year against PRRSv (modified-live vaccine without adjuvant). Replacements are sourced from other units, and all animals entering the farm are vaccinated against PRRSv.

The earliest clinical signs became apparent around the time of weaning. These included an unacceptable percentage of stillborn piglets, a high percentage of runts, non-specific diarrhea, loss of condition, nervous signs, arthritis and an increased mortality rate, all of which failed to respond to treatment with antibiotic (amoxicillin in the drinking water and by injection).

PRRS was confirmed by PCR in 1, 2, 3, 4 and 5 week-old animals. Samples from affected piglets revealed florfenicol-sensitive isolates of Streptococcus suis and Haemophilus parasuis.

The existing in-feed antibiotic treatment (100 ppm tiamulin + 80 ppm colistin in feed for 6 weeks after weaning), a previously tested schedule (1), was changed to 80 ppm florfenicol (2 kg/Tm Nuflor® 40 mg/g Premix for Swine) fed over the same period. The results of the two systems were compared, the previous treatment acting as a control for the florfenicol regime.

Results
Nursery phase: Mortality rates fell from 3.7% to 1.8%. The percentage of runts decreased from 7% to 2%, and the uniformity of the batches sent to slaughter improved. No differences were found for Average Daily Gain ADG (294 g/day). The economically important results are shown in Table 1. The number and cost of treatments needed to be given via the drinking water or by injection was reduced (-1.17€).

Table 1: Economic results in the nursery phase

<table>
<thead>
<tr>
<th>Euro/piglet</th>
<th>NUFLOR® Premix</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed</td>
<td>7.8</td>
<td>7.58</td>
<td>+0.22</td>
</tr>
<tr>
<td>Treatments (water &amp; injectable)</td>
<td>1.04</td>
<td>2.20</td>
<td>-1.17</td>
</tr>
<tr>
<td>Fixed costs</td>
<td>3.49</td>
<td>3.71</td>
<td>-0.22</td>
</tr>
<tr>
<td>Cost per piglet</td>
<td>26.34</td>
<td>28</td>
<td>+1.66</td>
</tr>
<tr>
<td>TOTAL</td>
<td>38.67</td>
<td>41.48</td>
<td>-2.82</td>
</tr>
</tbody>
</table>

Fattening phase: The mortality rate from historical farm records was 7%. In the florfenicol-treated group (3600 animals) the mortality rate was reduced by 4.5%. The feed conversion efficiency improved from 2.79 to 2.73, and the ADG increased from 638 to 700 g/day. The economically important results are shown in Table 2.

Table 2: Economic results in the fattening phase

<table>
<thead>
<tr>
<th>Euro/piglet</th>
<th>NUFLOR® Premix</th>
<th>Control</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feed</td>
<td>61.93</td>
<td>65.02</td>
<td>-3.09</td>
</tr>
<tr>
<td>Treatments (water &amp; injectable)</td>
<td>1.7</td>
<td>2.18</td>
<td>-0.48</td>
</tr>
<tr>
<td>Fixed costs</td>
<td>14.09</td>
<td>15.91</td>
<td>-1.82</td>
</tr>
<tr>
<td>Cost per piglet</td>
<td>40.99</td>
<td>42.15</td>
<td>-1.16</td>
</tr>
<tr>
<td>TOTAL</td>
<td>118.71</td>
<td>125.26</td>
<td>-6.55</td>
</tr>
</tbody>
</table>

The total saving for the group treated with Nuflor®40 mg/g Premix for Swine, over the course of the whole production cycle, was 9.37 € per pig.

Discussion
Piglets are susceptible to respiratory and digestive conditions in those production pyramids in which PRRSv has led to immune destabilization. This and severe secondary bacterial complications badly affect production.

This trial demonstrated that the use of a broad-spectrum antibiotic such as Nuflor®40 mg/g Premix for Swine, to which the most important respiratory bacteria are highly sensitive, is an effective solution. Both health and productivity improved throughout the production cycle, resulting in considerable economic benefits.

References
Usage of homeopathy as treatment for several disorders in pigs in an organic production system

Roberto G. Martinez; Marisol Esquivel; Enedina Silva; Jorge R. Lopez; Mario E. Haro; Roberto Martinez-Rodriguez
Facultad de Medicina Veterinaria y Zootecnia. Universidad nacional Autónoma de Mexico, Mexico, DF, Mexico

Introduction
The necessity of healthy food creates different systems of production; such as the case of organic production. Homeopathy medicine is ideal for this type of production owing to it is a medicine treatment that respects the natural reactions of the organism, and it is considered as a safe therapy par excellence. This is based on “The principle of Similarity”, and in order to this principle works it is necessary to have the infinitesimal doses which are: The substances which in considerable doses are able to provoke in healthy individuals clinical manifestations, they are able to eliminate such manifestations in an unhealthy individual if they are prescribed in small doses.

Material and Methods
This research was carried out in a farm localized 100 km northwest Mexico City, in an area which was adapted for the hosting sows in an organic production system. In this area were 15 breeding sows with different farrowing number and once farrow the piglets. All the animal were examined twice a day in order to identified any health problem and be able to implement a specific treatment. The following diagnostics and treatments were carried out:

- Sows underwent a change of management and grouping, with treatment based on Aconitum napellus and Carbo vegetalis 30 centesimal (c), administered twice a day, by 18 days.
- Abscess in teats, in shoulder and in ham of an adult sow. Treatment Silicea terra 30c (three times per day) and Silicea terra 200c (every three days) from 5 to 20 days.
- Banged sows. Arnica Montana 30c (twice a day) per 18 days.
- Sow with severe burn in one foot. Belladona atropa 30c (twice a day) Cantharis 6x (topic) once a day.
- Obstetrical problems, retention of piglets, yellow vaginal secretion with bad smell and almost non appetite. Caulophyllum 30c, Belladona atropa 30c and Arnica Montana 6c (every 2 hours and decreasing the frequency until twice a day).
- Respiratory disorders in piglets from 3 to 15 day of age and in one adult sow. Aconitum napellus and Belladona atropa 30c (three times a day per 4 days).
- Suckled piglets from 3 to 20 days, having yellow diarrhea. Arsenicum album 30c (three times a day, form 2 to 3 days).
- Castration injuries, Dye madre de caléndula once a day per 2 days.
- Prevention of anemia ferropriva. Ferrum metallicum 6c (twice a day).

Results
In connection with the banged and under stress sows after the weaning there were a reaction in all of them (15 animals). Talking about the abscess it was a reaction in 2 out of 3 sows (66.6%). The burnt sow treated with Belladona and Cantharis responded favorably. All of the sows with postpartum disorders responded favorably (100%). The combination of Aconitum and Belladona had a response of respiratory disorders in 34 out of 40 piglets (84%). Arsenicum alba had favorable response in suckled piglets with diarrhea, 14 out of 15 piglets (93%). None of the piglets had anemia.

Discussion
The results of this research carried out with the objective, they proved that it is possible to use homeopathy as a treatment of individual disorders in animals in an organic raising system. At the same time it is an alternative to the application of prophylactic treatments in biggest populations of pigs. The implementation of the treatment did not show any problem with management or containment of the animal.

References

Research financed by PAPIIT IN212008.
Efficacy of Denagard 20% Injection for Treatment of Polyarthritis in Nursery

Sasiwimon Talummuk; Penchan Chaiyanate; Metta Makhanon
Novartis (Thailand) Limited, Bangkok, Thailand

Introduction
Polyarthritis in suckling pig to nursery pig are very common clinical signs caused by pathogens including Mycoplasma hyorhinis (MHR), Haemophilus parasuis, and Streptococcus suis. These respiratory pathogens are transmitted from sows to piglets by direct contact. Infected piglets can be carriers after weaning (4). Early treatment by injection is the state-of-the-art method for effective control of polyarthritis caused by the listed pathogens. Tiamulin provides pronounced effect for treatment of Mycoplasma and Gram positive bacteria like Streptococcus suis due to MIC studies (2, 3). However, there are many sources of Tiamulin injection in Thailand. The objective of this study is to compare the efficacy of Denagard® 20% injection, original Novartis-Sandoz, and the local generic tiamulin injection for treatment of polyarthritis in nursery (1).

Materials and Methods
Farm history: A farrow to fattening farm was affected by serious polyarthritis problems, 20-30% mobility rate and 5-10% mortality rate from suckling piglets to nursery (Fig.1). Preventive program was water treatment with amoxicillin after weaning for 5-7 days. Pigs show minor response.

20 pigs with severe swollen joints and respiratory signs were selected and divided into two groups. Group 1 was treated by Denagard® 20% injection and Group 2 was treated by generic tiamulin injection for three days. Nasal swabs were collected from all pigs before onset of treatment to confirm mycoplasma infection. Joint diameter of four legs was measured by vernier clipper before the first tiamulin injection (day 1), the third injection (day 3) and two days after withdrawal of treatment (day 5). pH-value of the two different tiamulin injection products was measured. Nursery signs of pain after injection was observed. Statistical analysis of the joint diameter was done by ANOVA at p<0.05.

Results
MHR was isolated from all nasal swab samples. pH of Denagard® 20% injection is 8.5 while the generic tiamulin is 2.2. Some of the pigs receiving tiamulin generic injection showed sign of pain..

Table 1 Mean Diameter of joint (inch) before, during and after the treatment.

<table>
<thead>
<tr>
<th>Legs</th>
<th>Observed day</th>
<th>Mean Joint Diameter (inch)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Denagard 20%</td>
<td>Tiamulin generic</td>
</tr>
<tr>
<td>Right fore leg</td>
<td>Day 1</td>
<td>2.73 +/- 0.33</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>2.53 +/- 0.21</td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2.56 +/- 0.25</td>
</tr>
<tr>
<td>Left fore leg</td>
<td>Day 1</td>
<td>2.76 +/- 0.39</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>2.70 +/- 0.34</td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2.50 +/- 0.25</td>
</tr>
<tr>
<td>Right hide leg</td>
<td>Day 1</td>
<td>3.21 +/- 0.56</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>2.96 +/- 0.41</td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>2.90 +/- 0.38</td>
</tr>
<tr>
<td>Left hide leg</td>
<td>Day 1</td>
<td>3.41 +/- 0.70</td>
</tr>
<tr>
<td></td>
<td>Day 3</td>
<td>3.12 +/- 0.59</td>
</tr>
<tr>
<td></td>
<td>Day 5</td>
<td>3.10 +/- 0.69</td>
</tr>
</tbody>
</table>

Discussion
The mean joint diameter of Denagard® 20% injection treatment group show a gradual decrease from the first to the last day of evaluation. Significant differences of joint diameter were found from three legs on day 3 and day 5. Interestingly, MHR carriers status can be detected in all pigs from nasal swabs. The acidic pH in generic formulation and kind of active ingredient used in the generic products can influence the performance and efficacy and cause pain in sick nursery pigs at the site of injection. From this study it can be concluded that based on the higher product performance Denagard® 20% Injectable application causes significant reduction of swollen joints in nursery pigs suffered from polyarthritis. Its significant efficacy is showed during three to five days after treatment.

References
Effect of Polyfil™ (8% Phosphorylcholamine and Vitamin B₁₂, A and E) Injection on Blood Composition and Chemistry of Gilts

Chanathip Thammakarn¹ Jamlong Mitchaothai²
¹. School of Animal Production Technology and Fisheries, Faculty of Agricultural Technology, King Mongkut’s Institute of Technology Ladkrabang, Ladkrabang, Bangkok, Thailand; ². Department of Clinic for Swine, Faculty of Veterinary Medicine, Mahanakorn University of Technology, Nong Chok, Bangkok, Thailand

Introduction
Supportive treatments to weak or sick pigs with efficient and feasible methods would lead to minimize the low pig production. In principle, phosphorylcholamine (PC) is a phosphomonoester playing important role in membrane biosynthesis (1). Vitamin A, E and B₁₂ are crucial vitamins for the metabolisms of pigs. Hence, this study was performed in order to evaluate the effect of administration of PC, vitamin A, E and B₁₂ (Polyfil™) on blood composition and chemistry of gilts.

Materials and Methods
Eighteen gilts were randomly selected for the present study. All experimental pigs were equally allotted into two groups; the control and the treatment. The pigs in the treatment group have got injection of Polyfil™ (Laboratorios Ovejero, S.A., Spain) 5 ml once a week for 3 times weekly, while the pigs in the control group did not get any administration. Blood samples were collected from all pigs in both experimental groups at before the start of this study and at 3 days after each Polyfil™ injection. All blood samples were analyzed for blood composition (erythrocyte concentration & indices and leukocyte concentration & proportion), thrombocyte concentration and blood chemistry (SGOT, SGPT, BUN, creatinine, calcium, phosphorus and total protein). The statistical analysis is Repeated Measurements.

Results
The results of the present study have been showed in the Table 1. There was no effect of the administration of Polyfil™ on erythrocyte concentration and indices (HB, MCV, MCH and MCHC), leukocyte concentration and proportion, thrombocyte concentration and blood chemistry (SGOT, SGPT, BUN, creatinine, calcium, phosphorus and total protein). The concentration of blood phosphorus and significantly lower (p<0.05) the level of BUN. However, there was no effect of the Polyfil™ administration on other studied blood chemistry (SGOT, SGPT, Creatinine, Calcium, Total protein).

Discussion
Most of measured valued fell in the normal rages (2). The composition of blood and erythrocyte indices were not affected by administration of Polyfil™, this might be explained that the ingredients in Polyfil™ improve only composition of cell membrane. The increase of phosphorus in blood would be the results of PC containing in Polyfil™, which directly increase in blood stream or more incorporation into blood cells. The lower BUN of gilts in the treatment group indicated lower urea production, which might be the results of more utilization of amino acids. Therefore, the administration of Polyfil™ in gilts increased blood phosphorus and lowers BUN.

Table 1 Blood composition and chemistry of all pigs

<table>
<thead>
<tr>
<th>Item</th>
<th>Group</th>
<th>Week</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC, × 10³/μl</td>
<td>Cont</td>
<td>7.30</td>
<td>7.39</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>6.89</td>
<td>8.00</td>
</tr>
<tr>
<td>HB, g/dl</td>
<td>Cont</td>
<td>13.33</td>
<td>12.93</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>12.61</td>
<td>13.32</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>Cont</td>
<td>59.28</td>
<td>54.37</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>61.57</td>
<td>52.12</td>
</tr>
<tr>
<td>MCH, pg</td>
<td>Cont</td>
<td>18.86</td>
<td>17.54</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>18.42</td>
<td>16.58</td>
</tr>
<tr>
<td>MCHC, %</td>
<td>Cont</td>
<td>30.07</td>
<td>32.29</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>29.97</td>
<td>32.41</td>
</tr>
<tr>
<td>WBC, × 10³/μl</td>
<td>Cont</td>
<td>15.48</td>
<td>12.18</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>12.16</td>
<td>12.11</td>
</tr>
<tr>
<td>Neutrophil, %</td>
<td>Cont</td>
<td>27.00</td>
<td>32.56</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
<td>23.44</td>
<td>29.22</td>
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<tr>
<td>Lymphocyte, %</td>
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<td>62.44</td>
<td>59.22</td>
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<td>Treat</td>
<td>68.71</td>
<td>62.89</td>
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<tr>
<td>Platelet, × 10⁴/μl</td>
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<td>11.00</td>
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<tr>
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<td>6.62</td>
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<tr>
<td>SGOT, IU/l</td>
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<td>38.31</td>
<td>34.28</td>
</tr>
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<td>Treat</td>
<td>50.13</td>
<td>35.35</td>
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<tr>
<td>SGPT, IU/l</td>
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<td></td>
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<td>45.68</td>
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<tr>
<td>BUN, mg/dl</td>
<td>Cont</td>
<td>20.92</td>
<td>19.48</td>
</tr>
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<td></td>
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<tr>
<td>Creatinine, mg/dl</td>
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<td>2.76</td>
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<td>2.75</td>
<td>2.72</td>
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<tr>
<td>Calcium, mg/dl</td>
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<td>9.47</td>
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<tr>
<td>Phosphorus, mg/dl</td>
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<td>7.71</td>
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<tr>
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<td>9.02</td>
<td>7.90</td>
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<td>Total protein, g/dl</td>
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<td>8.24</td>
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</tr>
<tr>
<td></td>
<td>Treat</td>
<td>8.65</td>
<td>8.55</td>
</tr>
</tbody>
</table>

Cont = Control group, Treat = Treatment group, NS = Not significance

Acknowledgements
The authors wish to thank Union Agriphar Co., Ltd.

References
Susceptibility of Streptococcus suis strains isolated from diseased pigs in Thai PRRSV positive swine farms to Ceftiofur

Angkana Tantituvanont2 Walaisiri Muangsiri2 Weree Niyomthum1 Thitima Triipitat1 Indhira Kramongthong1 Dachrit Nilubol1

1. Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand; 2. Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

Introduction

Ceftiofur, a broad-spectrum cephalosporin is approved for the treatment of swine respiratory disease including Streptococcus suis (S. suis). Although Ceftiofur effectively reduced mortality associated with PRRSV and S. suis1, several field investigations in Thailand have reported varying degree of success when ceftiofur is used to control S. suis infection in PRRSV infected pigs. Unsuccessful control in PRRSV infected herds could be due to increased antimicrobial resistance, decreased pharmacokinetic in PRRSV infected pigs2 and etc. Although the in vitro antimicrobial susceptibility of S. suis has been widely investigated, ceftiofur susceptibility of S. suis isolated from PRRSV positive swine herds has not been reported. The objective of this study was to investigate the Minimum Inhibitory Concentrations (MICs) of ceftiofur against S. suis isolated from Thai PRRSV positive swine farms.

Materials and Methods

10 PRRSV positive swine herds located in the Eastern, Western, Northern and Southern regions of Thailand were recruited into the study. The PRRSV status of All 10 herds was considered PRRSV stable/ inactive, which PRRSV viremic phase and clinical diseases displayed during nursery period. Seroconversion against PRRSV as measured by ELISA (Idexx, USA) was 6 – 8 weeks of age. Necropsy examination was performed monthly for 3 consecutive months on pigs displaying clinical diseases associated with PRRSV and S. suis including respiratory distress, swollen joints and convulsion. Lung, tonsil and joint fluid samples were subjected for S. suis isolation.

Bacterial (S. suis) isolation was performed on sheep blood agar. Suspected colonies were separated by colonial morphology and confirmed by biochemical characteristics including API20 and Polymerase Chain Reaction (PCR). Ceftiofur susceptibility testing was performed using an agar dilution technique according to the standardized method described by Clinical and Laboratory Standard Institute (CLSI)3.

Results

A total of 119 Streptococcus spp. isolates were recovered from 86 diseased pigs. The biochemical characteristics and PCR assay demonstrated that out of 119 Streptococcus spp. isolates, only 17 isolates were S. suis and 2 of 17 were S. suis type 2. MICs values ranged from 0.125 - 256 μg/mL (Table 1). Considered MICs values of Ceftiofur be ≤0.03 μg/mL, most of the S. suis isolates demonstrated a high degree of ceftiofur resistance. A low degree of resistance was found in only 2 herds.

Discussion

The results of this study indicated an increased level of ceftiofur resistance of S. suis isolated from Thai PRRSV positive herds especially herds located in high proximity area and high level of antimicrobial usage. Factors associated with increased ceftiofur resistance in PRRSV positive herds should be investigated. In addition, the ceftiofur pharmacokinetics-pharmacodynamics data and its clinical outcomes should be used to justify the optimum therapeutic regimen.

References

2. Tuntituvanont, A. 2009 JAC: 369 -373
3. NCCLS, 1999

Table 1

<table>
<thead>
<tr>
<th>No. of S. suis isolates</th>
<th>Regions</th>
<th>MIC (μg/mL)</th>
</tr>
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<tr>
<td>1</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>2</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>3</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>4</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>5</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>6</td>
<td>West</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>West</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>West</td>
<td>256</td>
</tr>
<tr>
<td>9</td>
<td>West</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>11</td>
<td>West</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>West</td>
<td>16</td>
</tr>
<tr>
<td>13</td>
<td>West</td>
<td>&gt;256</td>
</tr>
<tr>
<td>14</td>
<td>West</td>
<td>0.125</td>
</tr>
<tr>
<td>15</td>
<td>West</td>
<td>256</td>
</tr>
<tr>
<td>16</td>
<td>West</td>
<td>4</td>
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<tr>
<td>17</td>
<td>South</td>
<td>0.125</td>
</tr>
<tr>
<td>18</td>
<td>S. suis NCTC10234</td>
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</table>

* S. suis NCTC 10234: Standard Streptococcus suis capsular type 2
Pharmacokinetics study of medicated feed containing chlortetracycline (Aurofac®) with or without BMD® in concurrent PRRSV and Mycoplasma hyopneumoniae – infected pigs

Dachrit Nilubol, Indhira Kramongthong, Thitima Tripipat, Mark Eastaugh, Ratchai Leethochawalit, Angkana Tantituvanont

1. Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand; 2. Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand; 3. Alpharma Pharmaceuticals (Thailand) Ltd., Bangkok, Thailand; 4. Alpharma Animal Health (Beijing) Trading Co, Ltd, Singapore, Singapore

Introduction
Several investigators have reported a synergistic effect for BMD and CTC resulting in decreased resistance of several pathogens (1, 2). Our previous studies suggest that the use of CTC in combination with BMD at the day of infection results in the significant reduction of lung lesion associated with Mycoplasma hyopneumoniae induced pneumonia (3). The objective of the study was to investigate the pharmacokinetics of Chlortetracycline when fed in combination with BMD in pigs co-infected with PRRSV and Mycoplasma hyopneumoniae.

Materials and Methods
Ten 3 to 4 week-old PRRSV and Mycoplasma hyopneumoniae negative pigs were randomly assigned with stratification by weight to 2 groups (A and B) of 5 pigs each. Pigs in both groups were challenged with both PRRSV and M. hyopneumoniae at 0 days post infection (DPI). While PRRSV was administered to pigs intranasally, M. hyopneumoniae was given to pigs intratracheally. While group A received medicated feed containing chlortetracycline (Aurofac®, Alpharma Animal Health, Thailand) at dosage 20 mg/kg BW and (BMD®, Alpharma Animal Health, Thailand) at dosage 33 ppm, group B received medicated feed containing only chlortetracycline. All medicated groups received medicated feed from 0 through 14 DPI (14-day total).

The pigs were gruel-fed twice a day at 600 and 1200 hrs. The dosages of CTC and BMD given to the pigs were 20 mg/kg BW per day and 33 ppm per kilogram of feed intake per day, respectively. The total amount of the drugs administered per day was calculated and separated into half to provide the pigs twice a day with gruel feed.

On 3 and 7 DPI, blood was serially collected from the same pigs at 0, 1, 2, 4, 6, 8, 12, 16, and 24 hours post medication (starting at 600 hrs and finishing at 600hrs next day) into heparinized tubes. Plasma was separated and stored in 80 °C until analysis. All plasma samples were determine the concentration of CTC. The plasma concentrations of CTC were analyzed using a validated high-performance liquid chromatography assay. Plasma concentration data of CTC were subjected to non-compartmental analysis based on statistical moment theory. All pharmacokinetic calculations were performed using linear modeling software (WinNonlin Version 3.2, Pharsight, California, USA).

Results
Pigs administered with the combination of CTC and BMD showed similar plasma drug concentration to pigs administered with CTC alone on 3 and 7 DPI. Although the average plasma CTC concentration of pigs administered with the combination of CTC and BMD was higher than that of pigs administered with CTC alone, the difference was not statistically significant. The average plasma chlortetracycline concentration of infected pigs was similar to that of non-infected pigs. There was no significant difference in Cmax, AUC, t1/2z and 1z between the two treatment groups (p >0.05). No significant differences in pharmacokinetic parameters were observed in pigs administered with either chlortetracycline alone or in combination with BMD (p >0.05) on 3 and 7 DPI. However, longer half-life was observed in the non-infected pigs administered with a mixture of CTC and BMD (26.1 h) compared to CTC alone (17.6 h).

Conclusion
The results showed that administering BMD in combination with chlortetracycline had slightly influence on chlortetracycline absorption. BMD showed to affect the elimination of chlortetracycline in the non-infected pigs, although the half-life values were not significantly different between pigs given CTC alone or in combination with BMD.

References
1. Winkelman, N. 2001 AASV; 77-82.
3. Nilubol, D. 2008 IPVS
Evaluation of the Pulmotil® premix effect on production parameters of sows and their litters in a commercial farm on the sisal zone in Yucatan, Mexico

M Carvajal1 J López1 J Rodriguez2 P Gómez2 C Quijano2 M Quijano2 M Noh3 J Hernández1

1. Elanco® Animal Health, León, GTO, Mexico; 1. Facultad de Medicina Veterinaria y Zootecnia Universidad Autonoma de Yucatan, Merida, YUC, Mexico; 3. Private practice, Merida, YUC, Mexico

Introduction
Previous studies have shown that the use of antibiotics in sows during the lactation diets reduces problems associated with infections peripartum and improves reproductive behavior. It reduces the transmission of pathogens of the sows to the piglets improving the health of these (1). This practice increases the survival of piglets and the produced kg per week at weaning and the finishing (2).

The objective of this study was to assess the effect of the use of Pulmotil® (Tilmicosin) in females during the stage of lactation on their litters productive parameters.

Materials and Methods
A study was conducted in a pig farm with 900 sows in the state of Yucatan, México. Animals were positive to diseases related to respiratory and gastro enteric signs. The total of born piglets from six groups of sows was studied. Each group was formed with 40 sows. The groups were divided according to treatment: 3 groups received 300 g of Tilmicosin (Pulmotil®) + 200g sulfamethoxazole and 50 g of Trimethoprin/ton of food. Other 3 groups received a premix based on 400 g of Oxytetracycline + 200 g of sulfamethoxazole and 50 g of Trimethoprin/ton (Other). Both treatments were managed in the diet a week before birth and during lactation. The piglets were individually identified and compared the weight to the birth, weaning, daily gain, and mortality. Data were analyzed in computing programs: SPSS 15.0 and WinEpiscope 2.0.

Results and Discussion
The average birth weights of piglets from sows of both treatments were compared and there was no significant difference (p=0.144). The mortality rate of piglets of Pulmotil® group and the other group was 2.9 % y 3.4% respectively. Although there is epidemiologic association between the treatment and mortality rate (OR=0.78), there was not significant differences because the confidence interval include the number one (IC=0.49 <OR<1.26).

The average weaning weights of piglets were compared observing a better performance in the Pulmotil® group (9.61 kg). The average days of lactation of sows were 20.70 day for Pulmotil® group and 19.98 days for the other group (table 2).

Table 1. Comparison of birth weight and weaning of pigs of both groups

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean (kg)</th>
<th>Standard deviation</th>
<th>Coefficient variation</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Birth</td>
<td>1229</td>
<td>1.420</td>
<td>0.322</td>
<td>22.68%</td>
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<tr>
<td>Other</td>
<td>1092</td>
<td>1.440</td>
<td>0.352</td>
<td>24.88%</td>
<td>0.144</td>
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<tr>
<td>Weaning</td>
<td>1147</td>
<td>6.866</td>
<td>1.383</td>
<td>20.14%</td>
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</tr>
<tr>
<td>Other</td>
<td>1022</td>
<td>6.242</td>
<td>1.508</td>
<td>24.17%</td>
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</tr>
</tbody>
</table>

The weight at 6 weeks of age was compared observing a better performance in the Pulmotil® group (9.61 kg) in contrast to the other group (8.37 kg). These weight were fitted to 39.9 days of age and 1.3 kg of weight birth; p= 0.000. The mortality rate to 6 week age was lower in the Pulmotil® group although there was not a significant difference.

Table 2. Comparison of gain weight of pigs during lactation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Weight gain in the period</th>
<th>Average daily gain</th>
<th>Lactation days</th>
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<tr>
<td>Pulmotil®</td>
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<td>4.790</td>
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</table>

The weight at 6 weeks of age was compared observing a better performance in the Pulmotil® group (9.61 kg). The average days of lactation of sows were 20.70 day for Pulmotil® group and 19.98 days for the other group (table 2).

Table 3. Comparison of weight gain of pigs during growing period.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weight average at sold (6 weeks)</th>
<th>Weights average at 10 weeks</th>
<th>Daily weight gain (born to 40 days)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Pulmotil®</td>
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<td>30.85**</td>
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</tr>
<tr>
<td>Other</td>
<td>8.370*</td>
<td>30.40**</td>
<td>175gr</td>
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</tr>
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</table>

* Weight at sold (6 weeks) fitted to 39.9 days and considering 1.3kg at birth
** Average weight fitted to 74 days considering 1.4 kg of birth weight.

Conclusion
It can be concluded that addition of Pulmotil® to the diet of the sows prior and during lactation period had a significant effect in the performance of their litters during lactation and weaning periods. As consequence a better performance is expected in the growing and finishing periods.

References