Duration of effectiveness of tulathromycin injectable solution in an *Actinobacillus pleuropneumoniae* respiratory-disease challenge model in swine

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Summary

Objective: To evaluate the duration of effectiveness of a single intramuscular injection of tulathromycin in a swine respiratory-disease challenge model using intranasal inoculation of *Actinobacillus pleuropneumoniae* serotype 5.

Materials and methods: Two hundred and forty female and castrated-male crossbred pigs were randomly assigned to six treatment groups and housed in 20 pens of 12 pigs per pen (two pigs per treatment per pen). On each of Days -11, -9, -7, -5, and -3, two pigs per pen were administered tulathromycin intramuscularly at 2.5 mg per kg body weight. Pigs assigned to the control group received no treatment. On Day 0, all pigs were challenged intranasally with highly virulent *A pleuropneumoniae* serotype 5. Each pig was assessed for general health and evaluated for abnormal respiration and attitude 9 hours post inoculation and at least daily until trial termination (Day 7). Necropsies were performed on pigs that died or were euthanized and on all surviving pigs on Day 7.

Results: With the exception of Day -11, pig removal rates (death and euthanasia) in the tulathromycin groups were significantly less than in the control group ($P < .05$). Additionally, the weighted percentages of total lung lesions for pigs administered tulathromycin on Days -5 (16.8%) and -3 (10.5%) were significantly less than that of the control group (27.5%; $P < .05$)

Implication: A single intramuscular dose of tulathromycin may provide up to 9 days of protection against death and severe morbidity caused by *A pleuropneumoniae* in pigs.

Keywords: swine, *Actinobacillus pleuropneumoniae*, tulathromycin, removals, lung lesions

Received: June 4, 2007
Accepted: December 13, 2007

Resumen - Duración de la eficacia de la solución inyectable de tulatromicina en un modelo de reto de enfermedad respiratoria con *Actinobacillus pleuropneumoniae* en cerdos

Objetivo: Evaluar la duración de la eficacia de una inyección intramuscular única de tulatromicina en un modelo de reto de enfermedad respiratoria porcina utilizando inoculación intranasal con *Actinobacillus pleuropneumoniae* serotipo 5.

Materiales y métodos: Doscientos cuarenta cerdos comerciales, hembras y machos castrados, se asignaron aleatoriamente a seis grupos de tratamiento y se alojaron en 20 corrales con 12 cerdos por corral (dos cerdos por tratamiento por corral). En cada uno de los Días -11, -9, -7, -5, y -3, se administró tulatromicina intramuscularmente a dos cerdos por corral a 2.5 mg por kg de peso corporal. Los cerdos asignados al grupo control no recibieron tratamiento. En el Día 0, se retó a todos los cerdos intranasalmente con un *A pleuropneumoniae* serotipo 5 altamente virulento. Se valoró la salud general y se evaluó la respiración anormal y la actitud de cada cerdo 9 horas después de la inoculación y al menos diariamente hasta el final de la prueba (Día 7). Se realizaron necropsias a los cerdos que murieron o fueron eutanasiados y a todos los cerdos sobrevivientes en el Día 7.

Resultados: Con la excepción del Día -11, los índices de cerdos retirados (muerte y eutanasia) en los grupos de tulatromicina fueron significativamente menores que en el grupo control ($P < .05$). Además, los porcentajes ponderados de lesiones pulmonares totales en cerdos a los que se les administró tulatromicina en los Días -5 (16.8%) y -3 (10.5%) fueron significativamente menores que los del grupo control (27.5%; $P < .05$)

Implicación: Una dosis única intramuscular de tulatromicina puede proveer hasta 9 días de protección contra la muerte y morbilidad severa causada por *A pleuropneumoniae* en cerdos.

Résumé - Durée d'action d'une solution injectable de tulathromycine dans un modèle d'infection défi par *Actinobacillus pleuropneumoniae* chez le porc

Objectif: Évaluer la durée d'action d'une injection intramusculaire unique de tulathromycine dans un modèle d'infection défi utilisant une inoculation intra-nasale d'*Actinobacillus pleuropneumoniae* sérotype 5.

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This article is available online at http://www.aasv.org/shap.html.

Waag TA, Bradford JR, Lucas MJ, et al. Duration of effectiveness of tulathromycin injectable solution in an *Actinobacillus pleuropneumoniae* respiratory-disease challenge model in swine. *J Swine Health Prod.* 2008;16(3):126–130.

Matériels et méthodes: Deux cent quarante porcs croisés (femelles et mâles castrés) ont été répartis au hasard à six groupes de traitement et logés dans 20 parcs de 12 porcs par parc (deux porcs par traitement par parc). Aux Jours -11, -9, -7, -5, et -3, deux porcs par parc ont reçu par voie intramusculaire de la tulathromycine à raison de 2.5 mg par kg de poids corporel. Les porcs assignés au groupe témoin n'ont reçu aucun traitement. Au Jour 0, tous les porcs ont été inoculés par voie intra-nasale avec un isolat très virulent d'*A pleuropneumoniae* sérotype 5. Un aperçu de l'état de santé général de chaque animal, de même qu'une évaluation de la présence d'une respiration anormale et du comportement ont été effectués 9 heures après l'inoculation et au moins une fois par jour jusqu'au moment de la fin de l'essai (Jour 7). Des nécropsies ont été effectuées sur les porcs qui sont morts ou ont été euthanasiés et au Jour 7 sur tous les porcs qui ont survécus.

Résultats: À l'exception du Jour -11, les taux de retrait des porcs (mort et euthanasie) dans les groupes traités à la tulathromycine étaient significativement inférieurs à celui du groupe témoin ($P < .05$). De plus, les pourcentages pondérés des lésions pulmonaires totales chez les porcs ayant reçu la tulathromycine aux Jours -5 (16.8%) et -3 (10.5%) étaient significativement inférieurs que ceux du groupe témoin (27.5%; $P < .05$).

Implication: Une injection intramusculaire unique de tulathromycine peut fournir jusqu'à 9 jours de protection contre une mortalité et une morbidité sévère associées à *A pleuropneumoniae* chez les porcs.

Tulathromycin (Draxxin Sterile Solution; Pfizer, New York, New York) is the first member of a new macrolide class of antimicrobials known as triamilides (semisynthetic derivatives of erythromycin), developed exclusively for use in veterinary medicine.[1] Formulated in an aqueous vehicle for intramuscular (IM) injection, tulathromycin administered as a single dose (2.5 mg per kg) is designed as a full course of therapy against gram-negative bacterial pathogens associated with the swine respiratory disease complex, including *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Bordetella bronchiseptica*, and *Haemophilus parasuis.*[2]

Following a single IM injection, lung concentrations, peaking at approximately 3.47 µg per g, are 61.4 times higher than plasma concentrations. Tulathromycin is slowly released from lung tissue, with an elimination half-life of approximately 6 days (142 hours).[3] In studies of commercial swine herds in Europe and North America, a single dose of tulathromycin had high levels of efficacy in cases of clinical bacterial respiratory disease.[2,4] Moreover, a single dose of tulathromycin has a cure rate comparable to multiple doses of ceftiofur sodium, enrofloxacin, florfenicol, or tiamulin.[4] The high and sustained concentrations of tulathromycin in lung tissue may underpin the high levels of efficacy that have been observed from a single dose.[3]

The objective of this study was to evaluate the duration of effectiveness of a single IM injection of tulathromycin in a swine respiratory-disease challenge model using intranasal inoculation of *A pleuropneumoniae* serotype 5.

Materials and methods

Study animals

Two hundred forty-five (245) clinically normal female and castrated-male crossbred pigs, approximately 6 weeks of age on arrival, were obtained from a commercial finishing unit and transported to the study site at Midwest Veterinary Services, Inc, Oakland, Nebraska. The pigs were sourced from a Canadian farrowing farm where sows were vaccinated against porcine reproductive and respiratory syndrome (PRRS) virus and swine influenza virus. Piglets had been vaccinated at weaning and 2 weeks post weaning with a combination *Mycoplasma hyopneumoniae* and *H parasuis* bacterin (Suvaxyn MH/HPS; Wyeth Animal Health, Guelph, Ontario, Canada). The study was conducted under the oversight of the Institutional Animal Care and Use Committee of Midwest Veterinary Services.

Exclusion criteria

Prior to initiation of the study, all pigs were acclimated for a period of 10 days in the study facility and were observed daily. Exclusion criteria included pre-existing disease or other physical conditions that might have interfered with the progression of *A pleuropneumoniae* infection or evaluation of the response to therapy, treatment with an antimicrobial agent within 15 days prior to challenge, and testing serologically positive for *A pleuropneumoniae* serotype 5. Except for the first 9 hours after challenge, pigs were removed from the study and euthanized if they exhibited advanced signs of respiratory distress, became moribund, or were unable to rise.

On the first day of treatment administration (Day -11), pigs included in the study were in good health, with rectal temperature ≤ 104°F. During the study, pigs that exhibited clinical signs of disease other than those associated with *A pleuropneumoniae* infection were examined by a veterinarian and the condition of these pigs was documented. Pigs that required therapy with systemic antimicrobial or anti-inflammatory agents were removed from the study. Pigs removed for reasons other than those related to *A pleuropneumoniae* infection were excluded from data analysis.

Study design

The study design was adapted from that of a study with similar objectives using ceftiofur crystalline free acid suspension.[5] Within 1 day of arrival, pigs were processed and individually identified by duplicate ear tags. Two hundred forty pigs were identified by number, those numbers were randomized, and the pigs were assigned to six treatment groups (40 pigs per treatment) according to a generalized block design (Table 1). The five remaining pigs, housed in a separate pen in the same room, were retained as replacements if required prior to treatment administration that began on Day -11. Pigs were evaluated daily for general health, beginning on the day of arrival, through the end of the study.

Processing did not include vaccination against PRRS virus or *A pleuropneumoniae*. On Day -11, blood samples were collected from 241 pigs to assess serological status to *A pleuropneumoniae* serotype 5. No tests were conducted for other respiratory pathogens.

On their assigned treatment days (Days -11, -9, -7, -5, and -3), pigs in Groups 2 through 6, respectively, were weighed and each was administered a single IM injection of tulathromycin in the neck at 2.5 mg per kg body weight. To monitor adverse product reactions, clinical observations were made on each pig prior to treatment administration and approximately

Table 1: Treatment groups in a study assessing duration of effectiveness of a single injection of tulathromycin* in a swine respiratory-disease challenge model using intranasal inoculation of *Actinobacillus pleuropneumoniae* serotype 5 in pigs approximately 8 weeks old

Group	No. of pigs	Treatment administered
1	40	Control (no tulathromycin administered)
2	40	11 days prior to challenge
3	40	9 days prior to challenge
4	40	7 days prior to challenge
5	40	5 days prior to challenge
6	40	3 days prior to challenge

* Tulathromycin administered intramuscularly at 2.5 mg/kg body weight.

2 hours afterwards. Pigs in Group 1 (controls) were not treated or sham injected.

All pigs in all treatment groups were challenged intranasally with *A pleuropneumoniae* on Day 0. As the *A pleuropneumoniae* inoculum was expected to produce moderate to severe disease, all pigs were observed by a veterinarian approximately 9 hours post inoculation for abnormal respiratory and attitude signs. No pigs were euthanized during the first 9 hours after challenge to avoid removing pigs treated with tulathromycin that might have recovered after temporary illness. After Day 0, pigs were assessed at approximately the same time daily for abnormal respiration and abnormal attitude, and those unable to rise without assistance were euthanized. The same veterinarian conducted all scheduled clinical assessments.

Pigs that were found dead or were euthanized were submitted for necropsy by a veterinarian masked to treatment. On Day 7, remaining pigs were euthanized and submitted for necropsy. Euthanasia was performed according to AVMA-approved methods,[6] using intravenous pentobarbital sodium followed by exsanguination.

Only personnel directly involved in administration of the tulathromycin and the study monitors had access to treatment records during the study. All other personnel participating in the study, including the clinical veterinarian responsible for assessing health status, were blinded to treatments until the end of the animal phase of the investigation. To assure blinding immediately after treatment, when pigs were being evaluated for adverse reactions, all pigs were observed at both time points each day treatments were administered.

Housing and management

Pigs assigned to Groups 1 through 6 were housed in 20 pens of 12 pigs each (two pigs per treatment group per pen) in one room of a cross-ventilated, temperature-controlled building. Pens had solid dividers and elevated expanded-plastic flooring over concrete manure pits. Feed space and drinkers were not shared between pens. Each pen measured 1.9 m × 2.4 m, allowing 0.38 m^2 floor space per pig. Pigs had ad libitum access to drinking water and to a nonmedicated grower ration.

Screening for *A pleuropneumoniae* serotype 5 antibodies

Serum samples were submitted to Kansas State University Veterinary Diagnostic Laboratory, Manhattan, Kansas, for testing using an ELISA that detects antibodies capable of binding to the capsular carbohydrate prepared from *A pleuropneumoniae* serotype 5. Results were reported as the antilogs of the adjusted optical densities. The laboratory-determined diagnostic cutoff values were negative < 2500; suspect = 2500 to 5000; and positive > 5000. Animals with negative or suspect tests were eligible for inclusion in the study.

Preparation of challenge inoculum

The challenge organism was a highly virulent *A pleuropneumoniae* serotype 5 isolate (APP ISU-200; Pfizer AHDRCC 26869) used in previously reported trials.[5] For tulathromycin, this challenge strain of *A pleuropneumoniae* has a minimum inhibitory concentration of 8.0 µg per mL in ambient air and 32.0 µg per mL in an enhanced CO_2 atmosphere.

The inoculum was prepared according to standard operating procedures of Midwest Veterinary Services. One vial of *A pleuropneumoniae* culture was removed from frozen storage, thawed in a cold water bath for approximately 5 minutes, and streaked on blood agar plates supplemented with a *Staphylococcus* species streak. After incubation overnight at 37°C, bacteria were identified by Gram staining and subsequently inoculated into tryptic soy broth with nicotinamide adenine dinucleotide and 2% horse serum. The culture was incubated at 37°C on a rotary shaker at approximately 100 rpm for 16 to 18 hours. The broth culture was tested by Gram staining to confirm purity (gram-negative rods), and colonies were selected with a sterile loop and streaked onto a blood agar plate supplemented with a *Staphylococcus* streak. After approximately 24 hours, the colony count was approximately 10^9 colony forming units (CFU) per mL (optical density approximately 1.5 at 630 nm). This suspension was diluted with tryptic soy broth to a concentration of 2×10^8 CFU per mL for the final inoculum. Final inoculum concentration was verified by viable plate counts before and after inoculation of pigs.

Administration of challenge inoculum

Pigs in Groups 2 through 6 were each manually restrained using a pig snare, then backed into a dog-sitting position with front legs extended. Four mL of a broth culture containing a total of 8.0×10^8 CFU of *A pleuropneumoniae* was administered by rapid intranasal inoculation (2 mL per naris) with a syringe upon inspiration.

Lung-lesion scoring

Lung lesions were both visually examined and physically palpated to determine the amount of consolidation or extent of other lesions in each lobe. The percent gross pneumonic lung involvement by lobe was recorded. Percent gross involvement of each lung lobe was estimated using the following ratios of individual lung lobes to total lung mass: left cranial 10%, left middle 10%, left caudal 25%, right cranial 10%, right middle 10%, right caudal 25%, and accessory 10%.[7] Percent was converted to proportion for analysis. The clinical veterinarian performing the necropsy examination of pigs that died or were euthanized before Day 7 determined lung-lesion scores, whereas scores for all

remaining pigs examined on Day 7 were determined by the study investigator. Lung lesions that differed from classical pleuropneumonia due to *A pleuropneumoniae* were cultured aerobically to identify other bacterial pathogens.

Data analysis

The primary efficacy variable was removal rate, with removal including both mortality due to challenge and euthanasia of moribund pigs. Removal rate was analyzed using the GLIMMIX procedure in SAS (SAS Institute, Cary, North Carolina). The procedure used the binomial error with a logit link. The model included the fixed effect of treatment and the random effects of pen and residual. The experimental unit for treatment was the animal.

The secondary efficacy variable was proportion of total lung lesions. Proportion of gross involvement of each lung lobe was weighted using the ratios of individual lung lobes to total lung mass as described. The weighted lung-lobe values were summed across lobes to yield the proportion of total lung with lesions and analyzed using a linear mixed model. The arcsine square root transformation was applied to proportion data prior to analysis. The model included the fixed effect of treatment and the random effects of pen and residual. The experimental unit for treatment was the animal. Lung-lesion scores for all pigs were included in the analysis, both for pigs that were recorded as deaths and pigs euthanized on Day 7.

Back-transformed least squares means were used as estimates of treatment means both for removal rate and percentage of total lung lesions. Standard errors of least squares means were estimated and 95% confidence intervals were constructed. A priori contrasts were used to assess treatment differences if the treatment main effects were significant. Significance was assigned to treatment differences with a P value < .05.

Results

Removal rate

During the 10-day acclimation period, one pig died and three others were excluded for general health reasons. Screening for *A pleuropneumoniae* serotype 5 revealed 227 negative and 14 suspect samples, thus all 241 pigs were eligible for the study.

The *A pleuropneumoniae* challenge model produced peracute, severe pleuropneumonia that resulted in the removal (death and euthanasia) of 31 pigs. Removals by treatment group are shown in Table 2. The removal rate for Group 2 (treated with tulathromycin on Day -11) was not significantly different from that for the untreated controls (Group 1). The distribution of those losses, however, differed numerically, in that 12 of the 13 removals in Group 1 occurred between Days 0 and 2, whereas only four of the eight removals in Group 2 occurred in this time period (Table 3). Removal rates for Groups 3, 4, 5, and 6 (treated with tulathromycin on Days -9, -7, -5, and -3, respectively) were significantly lower than the removal rate for the control group (Table 2). Also, removal rate was significantly lower for Group 6 (treated with tulathromycin on Day -3) than for Group 2 (treated on Day -11) (Table 2).

Lung-lesion scores

The proportion of total lung lesions is shown in Table 2. For pigs administered tulathromycin on Days -11 and -9, the weighted percentage of total lung lesions was not significantly different from that of pigs in the control group. For pigs treated on Day -7, the weighted percentage of total lung lesions tended to be lower than that of the control group (P < .10). Weighted percentage of total lung lesions was significantly less in Groups 5 and 6 compared to the control group; in Groups 4, 5, and 6 compared to Group 2; and in Group 6 compared to Group 3 (Table 2). All other treatment comparisons for lung lesions did not differ significantly. In one pig in Group 2 that died on Day 5 (16 days after injection of tulathromycin), *Pasteurella multocida* was cultured from lesions that were not typical of pleuropneumonia. Since pleuropneumonia was the primary lesion in this pig, the lungs were included in the analysis.

Discussion

Pharmacokinetic data[3] indicate that tulathromycin is metabolized slowly and most of the drug is excreted unchanged in feces and urine. These characteristics, together with its intrinsically slow release from cells, are thought to account for the sustained drug levels in lung and other tissue. Drug concentrations in lungs remain at levels higher than 1.2 µg per g for 10 days.[3] On the basis of these parameters, it could be predicted that tulathromycin would have a prolonged clinical effect and the potential for single-dose therapy.

In a previous clinical study, tulathromycin administered IM at 2.5 mg per kg provided effective single-dose treatment of pneumonia caused by an experimental challenge with *A pleuropneumoniae*.[8] In that study, administration of tulathromycin compared favorably to a 3-day regimen of ceftiofur sodium, a well-established therapy for respiratory disease caused by *A pleuropneumoniae*

Table 2: Removals* and proportion of total lung lesions by treatment in pigs challenged with *Actinobacillus pleuropneumoniae* on Day 0 and treated with a single intramuscular injection of tulathromycin†

Group	Day of treatment	Removals	Removal rate (%)	Proportion of lung with lesions (%)
1	NT	13	32.5^{a}	27.5^{de}
2	-11	8	20.0^{ab}	29.6^{d}
3	-9	3	7.5^{bc}	20.2^{def}
4	-7	3	7.5^{bc}	18.4^{eg}
5	-5	3	7.5^{bc}	16.8^{fg}
6	-3	1	2.5^{c}	10.5^{g}

* Removals included pigs that died or were euthanized when declared moribund by the attending veterinarian.

† Treatment groups described in Table 1.

^{abc} Values within a column with no common superscript differ (P < .05). Data were analyzed using a generalized linear mixed model that included the fixed effect of treatment and the random effects of pen and residual.

^{defg} Values within a column with no common superscript differ (P < .05). Data were analyzed using a linear mixed model that included the fixed effect of treatment and the random effects of pen and residual.

NT = not treated.

Table 3: Distribution of removals* by day of study in pigs challenged with *Actinobacillus pleuropneumoniae* on Day 0 and either not treated (Group 1) or treated with a single injection of tulathromycin† on Day -11 (Group 2)

Group	Day of study								Total
	0	1	2	3	4	5	6	7	
1 (n = 40)	0	9	3	0	1	0	0	0	13
2 (n = 40)	0	2	2	0	0	1	0	3	8

* Removals included pigs that died or were euthanized when declared moribund by the attending veterinarian.

† Tulathromycin administered intramuscularly at 2.5 mg/kg body weight.

in swine. Those results confirm that tulathromycin provides an effective single-dose therapy.

This study intended to provide the clinician with an estimate of the duration of the therapeutic effect of tulathromycin against *A pleuropneumoniae*. Nine pigs in the untreated control group were removed by Day 2, demonstrating the severity of the challenge. Removal rate, the primary decision variable in this study, indicated that tulathromycin was effective for up to 9 days against clinical disease associated with intranasal inoculation of highly virulent *A pleuropneumoniae* serotype 5. Lung-lesion data showed significant differences between untreated control pigs and pigs administered tulathromycin 3 and 5 days before challenge, and there was a tendency for a difference between control pigs and pigs treated with tulathromycin 7 days before challenge, further confirming prolonged clinical efficacy. The clinical response observed in this challenge model correlates with the pharmacokinetic data and supports the achievement of therapeutic effects with only a single injection.

Implication

A single IM dose of tulathromycin administered at 2.5 mg per kg can provide up to 9 days of protection against death and severe morbidity caused by *A pleuropneumoniae* in pigs.

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