THE CLINICAL RECOVERY OF FATTENING PIGS FROM RESPIRATORY DISEASE AFTER TREATMENT WITH TWO INJECTABLE OXYTETRACYCLINE FORMULATIONS

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SUMMARY

A double blind randomized clinical trial was performed with pigs suffering from clinical respiratory disease. The goal of the trial was to test the null hypothesis that the clinical recovery after treatment with two oxytetracycline injectables with different pharmocokinetic profiles (high peak concentration and low persistence versus low peak concentrations and long persistence) was similar. Fattening pigs (n=529) were treated intramuscularly with either product A or product B at a dose of 20 mg OTC per kg b.w. when they showed signs of acute pneumonia, i.e., coughing, tachypnoea or dyspnoea combined with a rectal temperature of 40°C or higher. When necessary, treatment was given again after 3 and/or 6 days. Both treatments resulted in a rapid fall in mean temperature and an improved clinical condition. In this trial no significant differences were found in clinical recovery between the two therapies as measured by group mean temperature, number of pigs requiring retreatment, and time to recovery. The conclusion that there was no important difference in clinical recovery between the treatment groups was made with a power of at least 90%.

INTRODUCTION

Acute respiratory disease is an economically important condition that affects pigs worldwide. In a recent Dutch survey, it was observed that most treatments (56%) in individual fattening pigs were applied for respiratory tract disorders (2). Oxytetracycline (OTC), a broad spectrum bacteriostatic drug, is generally used for treatment of affected pigs (6). Pneumonic pigs should be preferably treated parenterally, since both water and food consumption are significantly reduced during respiratory disease (12).

Several commercial OTC preparations exist, but few comparative clinical studies are available on which to base a rational choice between products. The choice for a particular product depends on the clinical efficacy, safety, residues, and other (commercial) criteria. One group of products shows a high initial peak plasma concentration (C_{max}) and a fairly low persistence ('conventional products'), while a second group of products ('Long-acting products') typically show a lower initial peak concentration but a prolonged plasma level (4, 5, 7, 14). These groups of products differ in excipient (e.g., solvents, additives) and concentration of OTC. These pharmaceutical factors affect the pharmacokinetic profile, tissue irritation, and persistence at the injection site (7-11, 16). The clinical importance of these differences in pharmacokinetic behaviour is not clear. When animals were experimentally challenged 48 hours after injection, prevention was better with long-acting preparation than with conventional products. This effect was not present when challenge occurred 24 hours after treatment (5). The importance of these findings for the treatment of respiratory disease under field conditions remains unclear. Comparative data on the clinical efficacy of both formulations was not available.

Therefore, the present study tested the null hypothesis that the clinical recovery rate of fattening pigs suffering from clinical respiratory disease is similar after treatment with two OTC products with different pharmacokinetic profile.

MATERIAL AND METHODS

Animals and trial sites

Animals from commercial fattening operations in two veterinary practices in central area of the Netherlands were eligible for entry into the trial when the owner observed an outbreak of clinical respiratory disease. Animals were only included in the trial when the estimated slaughtering date was at least 60 days after the date of the initial outbreak. Five hundred and twenty nine diseased fattening pigs from 11 commercial farms were included in the study. The pigs were mainly housed in pens with half-slatted floors containing 8-14 pigs. The fatteners treated in the trial were aged 12 to 22 weeks (21 to 80 kg) and suffered from acute signs of respiratory disease.

Experimental procedure

Pigs showing signs of respiratory disease were examined clinically. Rectal temperatures were measured using a digital thermometer. Clinical findings were registered. Individual pigs were assigned for treatment by a veterinarian (investigator A) when they showed signs of acute pneumonia, i.e., coughing, abnormal type of breathing, tachypnoea or dyspnoea, combined with a rectal temperature of 40 °C or higher. These pigs were included in the trial if at least two pigs in a pen could be treated. At the first visit, the pigs suffering clinically from a concurrent disorder, or showing a marked growth retardation were excluded from the trial.

The pigs were individually identified with ear tags and assigned alternately to one of the two treatment groups by a second investigator (investigator B). The first treatment in a pen was selected according to a random allocation by flipping of a coin. Absolute blindness throughout the trial was ensured by not informing either investigator A or the farmer of the treatment installed.

The pigs were re-examined three days and six or seven days after the first treatment by investigator A. An eventual second or third treatment was performed by investigator B when the pig still showed clinical signs of respiratory disea-

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se combined with a rectal temperature of 40°C or higher. All retreatments during the trial were recorded.

The farmer did not treat the experimental pigs during the first eight days of the trial; during the two weeks thereafter he recorded all treatments installed and recorded the clinical recovery after this two week period.

Treatments

The two OTC formulations used were Engemycine® 10% (to be called product A), containing 100 mg OTC/ml (Intervet International BV, the Netherlands; lot no. 89J17A and lot no. 90HO4A) and Terramycin®/LA (to be called product B), containing 200 mg OTC/ml (Pfizer; lot no 053B11A). The peak plasma OTC concentration (C max) of Engemycine® 10% is higher than that of Terramycin®/LA after intramuscular administration of the same dose in calves (7). In this species mean plasma OTC concentrations in excess of 0.5 µg/ml last longer after administration of Terramycin®/LA. OTC is detected more than 48 hours after intramuscular injection of Terramycin®/LA, and it is suggested that this is due to tissue irritation at the site of injection (7). Tissue irritation and drug persistence at the injection site of both formulations differ considerably, being more pronounced with Terramycin®/LA treatment (10). Both drugs were administered at a dose rate of 20 mg OTC/kg bw. Retreatments always consisted of the same OTC formulation as the first treatment. All injections were given deep intramuscularly in the neck region. First injections were on the right side, second injections, when needed on the left side and eventual third injections on the right side.

Statistical analysis

The necessary sample size was estimated to be approximately 534 animals. Sample size calculation (3) was based on an expected recovery of approximately 80%, a power of 90%, and a significance level of 5% to test the hypothesis of no marked difference (<10%) in clinical recovery between both treatments.

Body temperature data were visually checked for normality, and two-sample t-tests were used to analyse baseline comparability and recovery after treatment. The difference between treatment groups in the number of pigs requiring one, two, or three treatments was tested by using Fishers exact test (two-tailed) and the Mantel-Haenszel chi-square test on the 2x2 table frequencies stratified per farm.

Time to recovery was estimated for both treatments by using Kaplan-Meyer survival functions (3). The estimated recovery at any given day post treatment is the complement of the accumulated product of the probability of retreatment, given that the pig is still at risk of undergoing retreatment.

RESULTS

Clinical observations

The outbreaks of respiratory disease on each farm varied in clinical nature. Purulent nasal discharges was observed sporadically. On one farm nose deviations were seen in 15% of the treated pigs. Coughing was observed in 41% of the animals, and severe abdominal respiration in 41% of the animals. All 529 pigs treated showed an increased rate and abnormal type of respiration.

The group mean rectal temperatures of the affected pigs at the start of treatment in both treatment groups was 40.6°C ± 0.5, with a range from 40.0 to 42.4 °C. There was no significant difference in this baseline parameter between the treatment groups (t-test, P > .05). The mean rectal temperature results are shown in figure 1.

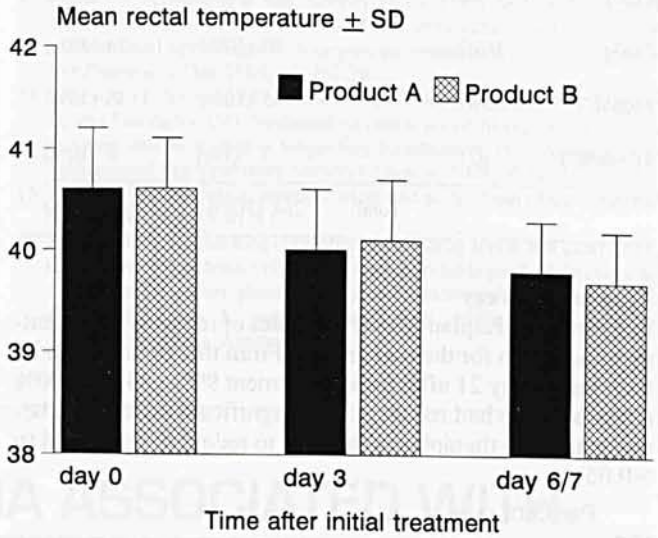

Figure 1. Mean rectal temperature (± SD) in the two treatment groups during the trial.

Mortality

Two pigs treated with A and one pig treated with B died during the study. These animals had responded positively to the treatment, and were considered to be cured from the pneumonia. They died between day 6/7 and day 21. On dissection, the pig receiving treatment B showed local peritonitis caused by an ileus. One out of two pigs receiving A showed a stomach ulcus; in the other animal no pathological lesions were observed. All three causes of death were considered to be not related to pneumonia.

Recovery following treatment

After both treatments the clinical condition of most of the pigs improved rapidly. Generally, the animals became more alert, their appetite improved, and the clinical signs of respiratory distress waned. In addition, after treatment with both formulations the group mean rectal temperature decreased to 39.9 °C ± 0.6. At the third clinical assessment the group mean temperature was 39.8 °C ± 0.6 and 39.6 °C ± 0.5, respectively. There were no significant differences observed in mean temperatures between both treatment groups at day 0, 3 and/or 6/7 (t-test, P > .5, in all three situations). The recovery after treatment is shown in table 1.

A proportion of 51% (Treatment A) versus 55% (Treatment B) of the treated pigs responded well to the first treatment. After day 7, 90% of the animals in both treatment groups had recovered. The number of pigs requiring three consecutive treatments was 10% for both treatment groups. The 95% confidence intervals (CI) for the differences in proportion includes zero, and thus the observed differences were not significant. Given the sample size in this trial, it can be stated, with a power of 90%, that the difference in clinical cure between products is less than or equal to 10%.

Table 1. Clinical recovery of pneumonic pigs after treatment with products A and B.

Treatment number (day)	Cure observed at day	Pigs recovered without relapse, n (%)	
		Treatment A	Treatment B
1 (d0)	d3	136 (52%)	148 (56%)
2 (d3)	d6/d7	80 (30%)	74 (28%)
3 (d6/d7)	> d6/d7	45 (18%)	43 (16%)
4 (> d6/d7)	d21	3 (1%)	0 (0%)
	Total:	264 (100%)	265 (100%)

Time to recovery

In figure 2 the Kaplan-Meyer estimates of recovery after treatment is shown for the two groups. From this figure it can be seen that at day 21 after initial treatment 99% (A) and 100% (B) of animals had recovered. No significant differences between the two therapies in the time to recovery was noted ($p > 0.05$).

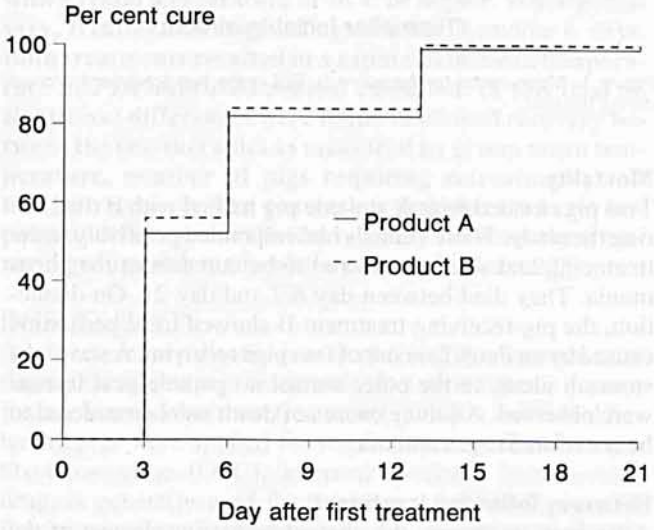

Figure 2. Kaplan-Meyer estimates of time to recovery after treatment in the two treatment groups.

DISCUSSION

In the present field trial, two frequently used OTC injectables with important differences in pharmacokinetic profile were compared. Pigs with acute pneumonia are usually treated on three consecutive days with conventional OTC or twice with 'long-acting' OTC injectables, at an interval of two or more days.

In our data no important difference in clinical recovery was observed between the two OTC injectables. In both groups clinical recovery, as judged by body temperature and clinical respiratory signs, was high. The observation of no important difference between two products does not necessarily imply a high efficacy of antibiotic treatment. Inclusion of a placebo group would allow calculation of antibiotic efficacy per se. However, inclusion of a placebo group was judged to be unwarranted for practical (farmer cooperation) and ethical reasons (3).

The results of this study apply to clinical recovery from outbreaks of respiratory disease of finishing hogs kept under commercial conditions. It is important to observe that no attempt was made to diagnose causative agents associated with the outbreak. Therefore it is not clear whether the treatment acted as a cure for acute bacterial infection or as a preventive measure against secondary bacterial infection during or following a viral episode. This uncertainty is common in current veterinary practice in commercial finishing operations.

In properly designed field trials some essential design requirements are concurrent controls, randomization, blindness and adequate statistical analysis (1,3). When screening veterinary literature, however, it was observed that most clinical trials either lack or do not report the basic requirements of trial design (1). The present study was designed to make a proper evaluation possible. Randomization and blindness of the trial was guaranteed and diminished the bias in response variables. Concurrent controls were included and sample size was sufficient to ensure a high power of the study.

The baseline comparability was evaluated by using body temperature data. Rectal temperature and the number of treatments proved feasible parameters to assess the clinical recovery rate of the antimicrobial therapy. Economic data such as growth retardation or slaughterhouse data were not evaluated.

The sample size was sufficient to conclude, with a power of 90% that there was no marked difference in clinical recovery between the two OTC therapies for the treatment of pneumonia under field conditions. In estimating the sample size it was assumed that the recovery rate after treatment would be approximately 80%. In this trial after one single treatment a recovery rate of 51% and 55% was found for products A and B, respectively. After two treatments, 90% of the pigs had recovered in both groups. This observation corresponds well with the overall high *in vitro* OTC susceptibility of porcine respiratory tract pathogens in the Dutch pig population (13).

Good veterinary practice implies a proper selection of effective but also safe drugs (9, 10). Criteria to select formulations include (clinical) efficacy, pharmacokinetic information on residues, tissue irritation and safety, and cost. From the viewpoint of public health policy, it is undesirable to have long OTC persistence in edible tissues and at the injection site (9, 15). An extensive irritation may be painful for the animal and is less acceptable with regard to animal welfare (9,10). In addition, financial loss at slaughter as a result of carcass downgrading caused by scars at the site of injection may be considerable (9). The results of this study should be weighed with these other pieces of information to decide on the formulation of first choice.

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HYPERLIPOPROTEINAEMIA ASSOCIATED WITH ATHEROSCLEROSIS AND CUTANEOUS XANTHOMATOSIS IN A CAT

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SUMMARY

Bilateral uveitis and multiple xanthomas (fat deposits in the skin) are described in a 3.5-year-old ovariohysterectomized female Persian cat. The cat had been treated for 2 years with corticosteroids. Examinations included a routine blood chemistry profile, radiographic examination of the thorax and abdomen, histopathological examination of multiple skin punch biopsies, and analysis of blood lipid components by cellulose-acetate electrophoresis and by preparative ultracentrifugation studies. Total lipid values were 23 g/l. Ultracentrifugation studies indicated strongly elevated VLDL and LDL fractions and a decreased concentration of the HDL fraction. Because of sudden blindness the cat was euthanized at the request of the owner. Autopsy revealed massive atherosclerotic changes in the large abdominal vessels, the wall of the aorta, and the coronary vessels. Although the exact pathogenesis remains uncertain, these unusual findings might be explained by a primary hyperlipoproteinaemia, complicated by long-term use of corticosteroids.

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CASE HISTORY

A 3.5-year-old ovariohysterectomized female Persian cat was referred to the Department of Clinical Sciences of Companion Animals of Utrecht University because of chronic bilateral anterior uveitis. The cat had been treated for the past 2 years with 0.1%[4] dexamethasone eye drops, twice daily. In addition to the eye problems, small nodular skin lesions had been present for 9 months. The nodules were located on the head and abdomen and in the inguinal region. Prednisone (1 mg/kg SID orally) for 8 months had not been effective.

Figure 1. Pinkish-yellow plaques in the temporal area.