ABSTRACT: The purpose of this study was to evaluate the efficacy of an oral solution of ketoprofen administered in drinking water at a lower dose as a complement to antimicrobial therapy in a mild outbreak of porcine respiratory disease complex. The study was performed with 120 pigs with rectal temperature between 39.9 and 41°C and at least 1 sign indicating porcine respiratory disease complex (dyspnea, cough, nasal discharge, or depression). Animals were randomly allocated in 2 groups (treated and control group). Animals in both groups received etiological therapy with doxycycline at 10 mg∙kg\(^{-1}\) in drinking water for 5 d. The animals in the treated group also received 1.5 mg∙kg\(^{-1}\) of ketoprofen during the first 3 d. The reduction in rectal temperature in the treated group was significantly greater during the days of ketoprofen administration and up to 1 d after the end of treatment (\(P < 0.05\)). The percentage of dyspneic animals was significantly less (\(P < 0.05\)) in the treated group from d 2 to 5 of the study. Also, a significant improvement regarding depression and cough was seen in the animals of the treated group. No statistically significant (\(P > 0.05\)) differences were evidenced in productive variables. In conclusion, oral treatment with ketoprofen at 1.5 mg∙kg\(^{-1}\) in combination with antimicrobial therapy was found to be a clinically effective approach in outbreaks of mild porcine respiratory disease complex.

Key words: clinical trial, drinking water, efficacy, ketoprofen, pigs, porcine respiratory disease complex
be unnecessary in mild respiratory conditions where a lower dose may suffice.

The purpose of this study is to demonstrate the efficacy of an oral solution of KTP administered in drinking water at 1.5 mg·kg⁻¹ for 3 consecutive days as a complement to antimicrobial therapy in a mild outbreak of porcine respiratory disease complex (PRDC).

MATERIALS AND METHODS

The study was designed in compliance with Directive 2001/82/EC and VICH – Good Clinical Practice (CVMP/VICH/595/98 – FINAL) and performed with previous authorization from the Spanish Medicines Agency.

Farm Selection

The study was performed at a commercial fattening pig farm located in Huesca, Spain, where an outbreak of mild respiratory infection consistent with PRDC had been diagnosed by means of necropsies and microbiological cultures. The presence of Mycoplasma hyopneumoniae was confirmed, complicated by the appearance of Bordetella bronchiseptica and Haemophilus parasuis.

Animals

It was presumed that efficacy of half the therapeutic dose could only be expected in animals with mild symptoms. Therefore, animals with temperatures above 41°C were intentionally excluded. Consequently, the inclusion criteria were animals with rectal temperature between 39.9 and 41°C and at least 1 of the clinical signs indicating PRDC, namely dyspnea, cough, nasal discharge, or depression. Finally, 120 crossbred fattening pigs of approximately 14 wk of age and between 24 and 57 kg BW satisfied these criteria and were included in the trial. The animals had not received any antibiotic or anti-inflammatory treatment that could affect the natural progression of the disease for the 7 d before the outbreak.

Treatment

All animals were individually identified and randomly distributed into 12 pens located on either side of the barn. The 6 pens on each side were assigned to either the treated or control group. Environmental conditions (temperature, ventilation, light, and dust) were similar on both sides of the barn.

Each group had an independent drinking water line. A stock solution with the proper volume of medication was prepared in a medication tank for each water line. A Dosatron proportional dosing pump (Dosatron International S.A.S., Bordeaux, France) was connected to each tank to ensure addition of a constant concentration of medication to the drinking water. Both groups received doxycycline hyclate (DOX; Doxydol; Fatro Uriach Veterinaria S.L., Barcelona, Spain) in the drinking water for a period of 5 d (d 1, 2, 3, 4, and 5) at a dose of 10 mg·kg⁻¹·d⁻¹. The treated group also received KTP in drinking water (Dinalgen/Danidol Oral Solution; Laboratorios Dr. Esteve S.A., Barcelona, Spain) during the first 3 d (d 1 to 3) at a dose of 1.5 mg·kg⁻¹·d⁻¹. Both medications were begun on d 1. No other medications were permitted during the study. Feed and water were supplied ad libitum. Samples of medicated water were taken throughout the study for both treatment groups to measure KTP concentration using high-performance liquid chromatography.

Study Design

Rectal temperature was measured at approximately 0800 and 1400 h (labeled as T1 and T2, respectively) on d 0 (baseline), 1 (T1 and T2), 2 (T1 and T2), 3 (T1 and T2), 4 (T1 and T2), 5 (T1), and 10 (T1) and was used as the main variable to assess and compare the efficacy of both therapeutic approaches. A Thermalog digital thermometer (Hartmann, Heidenheim, Germany), previously validated with a Testo thermometer (Testo, Lenzkirch, Germany), with a calibration certificate was used. Also, the presence or absence of dyspnea, cough, depression, and nasal discharge was recorded every day at T1 between d 0 and 5 as well as on d 10 with a specific dichotomic scale (presence = score 1; absence = score 0). Body weight was recorded individually on d 0 and 10 with a Gram M-SK-rev6 scale (Gram scales, Norcross, GA). Feed intake was recorded daily per pen from d 0 to 10 using a Digi DS-160 model scale (Digiweight, Chino, CA). Both variables were used to calculate the conversion rate between d 0 and 10. Water intake was recorded daily for each of the groups by means of a counter installed in each water line. Mortality was also registered daily throughout the study.

Blinding was achieved with the participation of 2 investigators, 1 for preparation and administration of the products (therapeutic investigator) and the other for monitoring and assessment of the clinical parameters (principal investigator).

Data Analysis

The experimental treatment unit was each group of animals located in the pens sharing the same water line. The experimental unit for efficacy assessment was each individual pig. All parameters were recorded individually for each pig, except the productive parameters of feed and water consumption, which were recorded per pen and treatment group, respectively. Healthy or seriously ill animals were not removed and shared pens with the
Oral ketoprofen in porcine respiratory disease

included animals during the entire experimental period. Therefore, excluded animals were also taken into consideration in the calculations of these variables.

The efficacy of both therapeutic approaches was assessed and compared on the basis of the differences in mean rectal temperature and the percentage of animals with a specific score for each of the secondary clinical variables as well as for mortality percentage, BW gain, and conversion rate.

The evolution of rectal temperature was analyzed by repeated measures ANOVA using a mixed model (PROC MIXED; SAS Inst. Inc., Cary, NC). Comparisons between treatment groups were performed for each time point by means of Student’s t test only when the main treatment effect was significant. Feed intake and BW gain were analyzed by means of an ANOVA model, adjusting for gender and baseline values, using PROC GLM of SAS. Categorical variables were analyzed using a χ² test of SAS.

RESULTS

The results of the main variable, rectal temperature, in both treatment groups are shown in Fig. 1. Mean rectal temperature decreased very rapidly in the treated group (−0.6°C d 1 at T1; P < 0.0001). In contrast, in the control group, the temperature increased to d 1 at T2 (+0.4°C; P < 0.0001) and from that day onward decreased slowly until d 5. Statistically significant differences (P < 0.05) between groups were found from d 1 to 4 of the study. On d 5 and 10, no significant differences were found.

Regarding the secondary clinical variables, significant differences were observed in the percentage of animals with dyspnea on d 2, 3, 4, and 5 of the study (P < 0.05) in favor of the animals treated with KTP (Fig. 2). Cough was not a very obvious clinical sign in the outbreak. However, significant differences (P < 0.05) were seen on d 2, 3, and 5 indicating that cough frequency had diminished in the treated group (Fig. 3). As shown in Fig. 4, nasal discharge improved very rapidly in both groups, being very low from d 2 onward. Significant differences (P < 0.05) were only found on d 3. Finally, the percentage of animals with depression in the treated group fell rapidly on d 2 whereas the reduction in the control group was more progressive (Fig. 5). These differences were statistically significant (P < 0.05) on d 2, 4, and 5.

Table 1 shows the productive parameters between d 0 and 10. No statistically significant differences (P > 0.05) were seen in ADG, ADFI, and G:F. Ketoprofen concentrations determined from water samples from the

Figure 1. Temperature evolution in both groups throughout the trial (mean ± SE). 1Pigs treated with 10 mg doxicicline (DOX) kg⁻¹·d⁻¹ for 5 d and 1.5 mg ketoprofen (KTP) kg⁻¹·d⁻¹ for 3 d. 2Pigs treated with 10 mg DOX kg⁻¹·d⁻¹ for 5 d. *P < 0.05.
Figure 2. Percentage of animals showing dyspnea in each group throughout the trial. ¹Pigs treated with 10 mg doxicicline kg⁻¹ d⁻¹ for 5 d and 1.5 mg ketoprofen kg⁻¹ d⁻¹ for 3 d. ²Pigs treated with 10 mg doxicicline kg⁻¹ d⁻¹ for 5 d. *P < 0.05; ns = no statistically significant differences.

Figure 3. Percentage of animals showing cough in each group throughout the trial. ¹Pigs treated with 10 mg doxicicline kg⁻¹ d⁻¹ for 5 d and 1.5 mg ketoprofen kg⁻¹ d⁻¹ for 3 d. ²Pigs treated with 10 mg doxicicline kg⁻¹ d⁻¹ for 5 d. *P < 0.05; ns = no statistically significant differences.
Oral ketoprofen in porcine respiratory disease

Figure 4. Percentage of animals showing nasal discharge in each group throughout the trial. ¹Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d and 1.5 mg ketoprofen kg⁻¹·d⁻¹ for 3 d. ²Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d. *P < 0.05; ns = no statistically significant differences.

Figure 5. Percentage of animals showing depression in each group throughout the trial. ¹Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d and 1.5 mg ketoprofen kg⁻¹·d⁻¹ for 3 d. ²Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d. *P < 0.05; ns = no statistically significant differences.
Table 1. Productive variables (mean ± SE) in the treated and control group

<table>
<thead>
<tr>
<th>Productive variables</th>
<th>Treated group¹</th>
<th>Control group²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADG, g</td>
<td>667 ± 24.1ª</td>
<td>640 ± 24.1ª</td>
</tr>
<tr>
<td>ADFI, kg animal⁻¹ d⁻¹</td>
<td>1.40 ± 0.063ª</td>
<td>1.27 ± 0.062ª</td>
</tr>
<tr>
<td>G:F, kg·kg⁻¹</td>
<td>0.507 ± 0.060ª</td>
<td>0.495 ± 0.060ª</td>
</tr>
</tbody>
</table>

¹Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d and 1.5 mg ketoprofen kg⁻¹·d⁻¹ for 3 d.
²Pigs treated with 10 mg doxicicline kg⁻¹·d⁻¹ for 5 d.

Table 1. Productive variables (mean ± SE) in the treated and control group

<table>
<thead>
<tr>
<th>Productive variables</th>
<th>Treated group¹</th>
<th>Control group²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADG, g</td>
<td>667 ± 24.1ª</td>
<td>640 ± 24.1ª</td>
</tr>
<tr>
<td>ADFI, kg animal⁻¹ d⁻¹</td>
<td>1.40 ± 0.063ª</td>
<td>1.27 ± 0.062ª</td>
</tr>
<tr>
<td>G:F, kg·kg⁻¹</td>
<td>0.507 ± 0.060ª</td>
<td>0.495 ± 0.060ª</td>
</tr>
</tbody>
</table>

A within a row, means without a common superscript differ (P < 0.05)

1.5 mg·kg⁻¹

whereas the other animal died during the follow up period due to causes unrelated to the respiratory process. No adverse events attributable to the products were seen throughout the study.

DISCUSSION

The differences in the main variable, rectal temperature, found during most of the experimental period showed that supplementation with KTP at 1.5 mg·kg⁻¹ is superior to treatment with DOX alone. Reduction in rectal temperature was significantly greater not only during days of KTP administration but also 1 d after administration was completed (d 4). Additionally, no fluctuations in rectal temperature were seen in the treated group, meaning that the concentrations of KTP achieved in blood were probably sufficient to keep temperature under control at all times. Improvements seen in the frequency of other clinical signs were statistically significant and also lasted even longer (d 4 to 5) than KTP administration. In particular, evolution of the percentages of dyspneic or depressed animals improved more rapidly and consistently in animals treated with KTP confirming that administration of NSAID, either alone or as a complement to antibacterial therapy of respiratory conditions, accelerates clinical resolution of the process previously described by other authors (Kopcha and Ahl, 1989; Deleforge et al., 1994; Balmer et al., 1997; Lockwood et al., 2003; Fraile et al., 2010). Also, the evolution of these parameters indicates that the dose of 1.5 mg kg⁻¹ is effective in these clinical situations.

For practical reasons, it was not feasible in this trial to include a positive control group receiving the full KTP dose (3 mg·kg⁻¹). In consequence, it would be difficult to speculate on whether or not these animals might have obtained further benefit from a greater KTP dose. Likewise, no conclusions can be drawn regarding whether 1.5 mg·kg⁻¹ would be similarly effective in case of severe outbreaks because in this trial all animals with rectal temperature above 41°C were excluded.

Also, comparisons with other trials are difficult given the lack of published, detailed clinical trials with oral KTP in similar clinical situations. In this sense, the results obtained in this trial are similar to our previous results in clinical trials with the use of either an injectable or an oral formulation at 3 mg·kg⁻¹, in which were detected significant differences in rectal temperature from d 3 and 2, respectively, although in these cases severe cases were not excluded (Sabate et al., 2012a,b). Also, Mustonen et al. (2011) did not find any differences in efficacy between 2 or 4 mg kg⁻¹ in the only published clinical trial comparing different KTP oral doses in pigs, although with a different indication, as well as in pigs challenged with Escherichia coli endotoxin (Mustonen et al., 2012). In a recently published trial, Fraile et al. (2010) also obtained a significant reduction in rectal temperature comparable to the one obtained in the present trial in an outbreak of respiratory disease after administering acetilsaliclyc acid at the full recommended dose (100 mg·kg⁻¹) together with oral DOX. These authors were unable to detect improvement in any of the clinical parameters studied (abdominal breathing, cough, and depression), possibly due to the reduced anti-inflammatory effects of acetilsaliclyc acid. Moreover, Salichs et al. (2012) used the same experimental model as Mustonen et al. (2012) to demonstrate that 1.5 mg·kg⁻¹ of KTP performed better than paracetamol or acetilsaliclyc acid as oral alternatives of NSAID for swine. Taking these data and the results of this trial into account, it is reasonable to anticipate that this dose may provide a satisfactory response in most clinical situations, especially when compared with the performance of the other available oral products for swine.

Finally, the evident clinical improvement of the animals treated with KTP did not translate into significant differences in the productive parameters. This was probably due to a low statistical power, because favorable tendencies were observed consistent with the clinical results.

Conclusions

The results of this study indicate that administration of an oral dose of KTP of 1.5 mg·kg⁻¹ in mild outbreaks of PRDC, in combination with antimicrobial therapy, is highly effective, accelerating clinical recovery and minimizing treatment costs.
LITERATURE CITED


