Oral ketoprofen is effective in the treatment of non-infectious lameness in sows

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ABSTRACT

The efficacy of ketoprofen in the treatment of non-infectious lameness in sows was examined in a double-blinded study. Two dose rates of oral ketoprofen were compared to placebo treatment over five consecutive days. Lameness was assessed with a five-grade scoring system prior to and on the last day of the treatment.

The rate of treatment success was 54.3% for the ketoprofen 4 mg/kg group (n = 46), 53.2% for the ketoprofen 2 mg/kg group (n = 47) and 20.8% for the pigs in the placebo group (n = 48). The difference between both ketoprofen groups and the placebo group was significant (P = 0.001), but there was no difference between the two ketoprofen groups (P = 0.78). Oral ketoprofen was well tolerated and no adverse events were observed. As lameness is a very common problem in sows, oral ketoprofen appeared to be a practical way to alleviate pain and improve the welfare of sows.

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Introduction

Lameness is a common problem among sows and gilts. It seldom causes death, but often leads to poor animal welfare and economic losses because of unplanned removals. Locomotor disorders have been the most common reason for culling sows in Denmark (Kirk et al., 2005) and Sweden (Engblom et al., 2008). In Finland, 9% of loose-housed sows and gilts were reported to be lame (Heinonen et al., 2006).

Locomotor disorders of lame pigs cause severe pain, and they need to be treated accordingly. In addition to obvious ethical considerations regarding pain alleviation, it should be kept in mind that milk production is diminished and piglet mortality increases when sows are in pain (Chen et al., 2008).

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) that has been used in human medicine to treat arthritis because of its anti-inflammatory and analgesic effects (Veyes, 1991). In Europe, parenteral ketoprofen is currently licensed for the treatment of porcine agalactia syndrome and for its anti-inflammatory, analgesic and anti-inflammatory actions related to respiratory infections in pigs when administered at a dose rate of 3 mg/kg intramuscularly (IM) (EMEA, 1996), but it is not licensed for the treatment of lameness in pigs. Orally administered ketoprofen has been reported to be absorbed well in this species and bioavailability was almost complete (Raekallio et al., 2008). The preferred dose of oral ketoprofen in pigs challenged with Escherichia coli endotoxin was 2 mg/kg (Mustonen et al., 2008).

Another NSAID, meloxicam, alleviated the signs of non-infectious locomotor disorders in pigs (Friton et al., 2003). However, while the efficacy of ketoprofen in treating orthopaedic problems has been reported in humans (Veyes, 1991), cattle (Longo et al., 1994), horses (Owens et al., 1995) and cats (Lascelles et al., 2001), there have been no reported studies on the efficacy of ketoprofen in alleviating pain and inflammation in locomotor disorders in swine.

The aims of this study were to examine the efficacy of oral ketoprofen, and to compare two oral doses (4 and 2 mg/kg) given for 5 days for the treatment of lameness caused by non-infectious musculoskeletal disorders in sows and gilts.

Materials and methods

This randomised, double-blinded, placebo-controlled, clinical field trial was conducted on 10 privately owned farms in southern Finland. The farms had a median number of 450 sows (range 80–1000). Three of the farms used deep litter bedding, two had solid concrete floors with a little straw, two had partially slatted concrete floors with no bedding, and three used fully slatted floors with no bedding.

A series of two study visits to each farm was carried out 1–4 times between February and October 2008. For the sample size calculation, the expected difference in efficacy between groups treated with ketoprofen and placebo was 25% (Friton et al., 2003). The required sample size was 47 animals in each group with a one-tailed test and with a statistical power of 80%. The field trial was conducted until the sample size required was achieved.

The study complied with Good Clinical Practice (GCP) guidelines, and the protocol was approved by the Ethical Committee of the University of Helsinki.
A total of 1955 sows and gilts (30–168 animals per herd), which had been inseminated at least once, were included in the first stage of the study. On small farms with <500 sows, all eligible loose-housed sows and gilts were examined for signs of lameness. In units with >500 sows, the owner presented the loose-housed animals eligible for inclusion according to the instructions of the investigators. In these large herds, the maximum number of animals that could be inspected within 1 day (an average of 104 sows) limited the number of animals included in the study. 

In the first stage, the investigator evaluated the movement of pigs (n = 1955) in groups for 2–5 min in their own pen. Some animals were examined on the gangway if their movements could not be adequately observed in the pen. A total of 282 animals with abnormal movements were selected to be examined individually. Two investigators independently assessed lameness using a five-grade lameness scoring scale (Table 1) while the animals walked on a hard, solid floor for a distance of at least 10 m. The animals with a lameness score > 2 identically assessed by both investigators independently were included in the study. 

In the second stage, a total of 141 lame animals on day 0 (n = 162). The lame leg was inspected and palpated. Rectal temperature was measured using a digital thermometer. The bodyweight (BW; kg) of the animals was calculated using the following formula: circumference (cm) x length (cm)/13,781 (Savage, 2004). The parity number was recorded from the farm data. 

Fourteen animals were excluded for one or more of the following reasons: fractures, infected leg wounds, a body temperature >39.5 °C or any other concurrent disease. In addition, seven animals were excluded because of protocol violation. The number of animals included in the final analysis varied between the farms from 5 to 31. A total of 141 animals (114 sows, 27 gilts) were included in the final analysis. On day 5, the last medication day, the study animals were re-examined in the same way as described above. 

Each lame animal was matched with one healthy control animal to compare the parameters measured from blood samples. The control animals (n = 141) were examined and sampled in the same way as the lame animals, but they were not treated.

### Blood sampling and laboratory analysis

A blood sample was taken from the saphenous or tail vein of each study animal the next day. The haemoglobin concentration, packed cell volume (PCV), erythrocyte and leukocyte counts were estimated. The haptoglobin concentration was determined by using the haemoglobin-binding assay for bovines (Makimura and Suzuki, 1982), with slight modifications (Heinonen et al., 2010).

### Treatments

The sows included in the study were allocated at random to one of the three treatment groups: (1) ketoprofen 4 mg/kg; (2) ketoprofen 2 mg/kg, or (3) placebo. Ketoprofen 4 mg/kg (Peroxon) was used as the test product for the dose 4 mg/kg and a mixture of Ketovet 4.2 mg oral powder and placebo in 1:1 ratio for the dose 2 mg/kg. The placebo contained 14 g of maltodextrine and 1 g of carmellose sodium. University Pharmacy of Helsinki manufactured the 2 mg/kg mixture and placebo and re-packed and labelled all sachets. Several sows had a parity of 4 or more (53.2% of the animals in the ketoprofen 4 mg/kg group, 55.2% of the animals in the ketoprofen 2 mg/kg group and 20.8% of the animals in the placebo group. The difference between both ketoprofen groups and the placebo group was significant (P = 0.001, CMH test stratified by farm), but the difference between the two ketoprofen

### Efficacy

The lameness scores of the animals in different treatment groups did not differ at the beginning of the study, on day 0 (Table 2). Mean changes in lameness scores from day 0 to day 5 are presented in Table 3 and the efficacy of treatment in different groups in Table 4. The treatment was considered successful for 54.3% of the animals in the ketoprofen 4 mg/kg group, 53.2% of the animals in the ketoprofen 2 mg/kg group and 20.8% of the animals in the placebo group. The difference between both ketoprofen groups and the placebo group was significant (P = 0.001, CMH test stratified by farm), but the difference between the two ketoprofen groups in Table 3.
groups was not significant (P = 0.78, CMH test stratified by farm). The treatment successes of the three parity groups did not differ (P = 0.21, CMH test stratified by farm).

A fully slatted floor alone had no direct impact on the success rate (P = 0.43), but the interaction between the treatment and the slatted floor was significant (P = 0.04, from the logistic regression model in which the ketoprofen groups were combined). With both of the floor types, the active treatment groups had better success rates than the placebo group, but the differences were more pronounced in the farms that had concrete or only partly slatted floors.

**Laboratory analysis**

Haemoglobin concentrations, PCV, erythrocyte and leucocyte counts, and haptoglobin concentrations were normally distributed. The blood values of the animals included in the final analyses were within the normal range or with only minor changes (Friendship et al., 1984) both before and after treatment (Table 5). No significant differences were detected between the groups.

**Discussion**

This study demonstrated that oral ketoprofen was efficient in alleviating the signs of non-infectious lameness in sows and gilts. Non-infectious diseases have been found to be a major cause of lameness in sows and gilts (Dewey et al., 1993; Heinonen et al., 2006; Engblom et al., 2008). Because locomotor disorders may cause severe pain, analgesia must be considered and lame pigs need to be treated appropriately. Early intervention and medication of sick animals is important, both for medical and animal welfare reasons; the prevention of problems is usually better than cure, and ethically more acceptable. Management factors have a major influence on the incidence of lameness at the farm level (Heinonen et al., 2006). However, although the risk of lameness can be reduced by good management and preventive actions, it could not be totally eliminated.

In the present study, there was no difference in efficacy between the two ketoprofen doses. The smaller dose was cheaper, easier to administer and may have caused a smaller risk of adverse effects (although this was not apparent). The findings support the use of ketoprofen in treating locomotor disorders in pigs. Lameness is also a common problem in piglets and will induce pain and reduce growth rates (Zoric et al., 2003). However, further pharmacological and economical studies are required before recommendations for the use of oral ketoprofen in piglets can be made, since pharmacokinetic differences may result in slower elimination and therefore retention of the drug, compared to mature pigs (Lees et al., 2004).

Food animal medication is under strict regulation by regulatory authorities. Ketoprofen belongs to Annex II of EEC Council Regulation 2377/90, which means that there is no maximum residue level (EMEA, 1996). The withdrawal period for a ketoprofen injection in the pig is 4 days due trace levels of residues at the injection site, whereas ketoprofen oral solution (which is the only orally administered NSAID licensed for pigs in any EU country) has a withdrawal period of 1 day for meat (Irish Medicines Board, 2010).

Lame animals often require NSAID medication for several days. In previous work, it was found that the efficacy of oral ketoprofen was similar to that of injectable meloxicam (Friton et al., 2003). Although injectable ketoprofen and meloxicam are not as irritating to the tissues as some other NSAIDs, they do cause local tissue damage after IM injection (Pyorala et al., 1999; Magyan and Glávits, 2007). Oral administration is therefore less painful and animal friendly for longer-term medication. However, the long term side effects of the treatment need to be elucidated. Some of our owners were doubtful about the oral administration of medicine to the sows and gilts at the beginning of the study but then discovered it was relatively easy to administer the medication orally, even though the animals were loose-housed in groups.

Diagnosing non-infectious lameness in sows by clinical examination is difficult (Dewey et al., 1993; Engblom et al., 2008). In most cases, post mortem examinations are needed to correctly diagnose the cause of lameness. In our study, diagnosis was based on a thorough clinical examination and analysis of blood samples. Any indication for antibiotics prior to, during or after the treatment was an exclusion criterion. Performing the lameness examination and making the sows walk was also difficult. In some cases, repeated walking was necessary, which could have had an influence on the degree of lameness. To minimise bias, both investigators assessed lameness scores independently and only the animals

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### Table 3

Average lameness scores and their mean changes in 141 lame sows and gilts before (day 0) and after (day 5) per oral ketoprofen (two dose groups) or placebo treatment for 5 days.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Animals</th>
<th>Day 0 Mean score (±s.d.)</th>
<th>Day 5 Mean score (±s.d.)</th>
<th>Mean change (±s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen 4 mg/kg</td>
<td>46</td>
<td>2.37 (0.53)</td>
<td>1.5 (0.98)</td>
<td>0.87 (0.98)</td>
</tr>
<tr>
<td>Ketoprofen 2 mg/kg</td>
<td>47</td>
<td>2.43 (0.50)</td>
<td>1.38 (0.97)</td>
<td>1.0 (1.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>48</td>
<td>2.52 (0.65)</td>
<td>2.08 (0.82)</td>
<td>0.44 (0.82)</td>
</tr>
</tbody>
</table>

Groups with different superscripts within the column differ significantly (P < 0.05).

### Table 4

Efficacy of treatment of 141 lame sows or gilts in three treatment groups: ketoprofen 4 mg/kg, 2 mg/kg and placebo orally for 5 days.

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Ketoprofen 4 mg/kg, number (%) of animals</th>
<th>Ketoprofen 2 mg/kg, number (%) of animals</th>
<th>Placebo number (%) of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>7 (15%)</td>
<td>10 (21%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Good</td>
<td>18 (39%)</td>
<td>15 (32%)</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Fair</td>
<td>4 (9%)</td>
<td>8 (17%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Poor</td>
<td>17 (37%)</td>
<td>14 (30%)</td>
<td>28 (58%)</td>
</tr>
</tbody>
</table>

### Table 5

Mean values (±s.d.) of haemoglobin concentrations, PCV, erythrocyte and leucocyte counts and haptoglobin concentrations of healthy control animals and lame sows or gilts receiving ketoprofen 4 mg/kg, 2 mg/kg or placebo.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment group</th>
<th>Control animals</th>
<th>Ketoprofen 4 mg/kg</th>
<th>Ketoprofen 2 mg/kg</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (gL)</td>
<td>Day 0</td>
<td>117 (12.0)</td>
<td>115 (11.2)</td>
<td>118 (13.0)</td>
<td>114 (11.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Day 5</td>
<td>114 (12.4)</td>
<td>113 (11.7)</td>
<td>113 (12.4)</td>
<td>112 (12.2)</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>PCV (L/L)</td>
<td>Day 0</td>
<td>0.36 (0.04)</td>
<td>0.35 (0.04)</td>
<td>0.36 (0.04)</td>
<td>0.35 (0.04)</td>
<td>0.4</td>
</tr>
<tr>
<td>Day 5</td>
<td>0.35 (0.04)</td>
<td>0.35 (0.04)</td>
<td>0.35 (0.04)</td>
<td>0.34 (0.04)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte counts (10^12/L)</td>
<td>Day 0</td>
<td>5.8 (0.7)</td>
<td>5.8 (0.7)</td>
<td>5.8 (0.7)</td>
<td>5.7 (0.7)</td>
<td>0.7</td>
</tr>
<tr>
<td>Day 5</td>
<td>5.7 (0.7)</td>
<td>5.7 (0.7)</td>
<td>5.7 (0.6)</td>
<td>5.6 (0.7)</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Leukocyte counts (10^9/L)</td>
<td>Day 0</td>
<td>12.9 (2.9)</td>
<td>13.1 (3.1)</td>
<td>13.8 (3.5)</td>
<td>12.8 (3.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>Day 5</td>
<td>12.6 (2.4)</td>
<td>12.8 (2.5)</td>
<td>13.7 (3.0)</td>
<td>13.0 (3.1)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Haptoglobin (mg/L)</td>
<td>Day 0</td>
<td>1878 (512)</td>
<td>1910 (611)</td>
<td>1707 (520)</td>
<td>1833 (766)</td>
<td>0.81</td>
</tr>
<tr>
<td>Day 5</td>
<td>1825 (530)</td>
<td>1702 (523)</td>
<td>1838 (569)</td>
<td>1802 (711)</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

whose lameness could be assessed accurately and identically by both investigators were included in the analysis.

The 20% efficacy of the placebo found in this work was similar to the placebo effect also reported by Friton et al. (2003). This is a well recognised phenomenon and has been reported to be approximately 30% in animal studies (Vasseur et al., 1995; McMillan, 1999; Munana et al., 2010).

In our study, the cause of non-infectious lameness was not determined, but in most cases was not severe and any minor injuries should heal quickly without intervention. The leukocyte count, haemoglobin concentration and PCV values are lower in healthy pigs than in those with an inflammatory process (Odink et al., 1990). Blood values were within the ranges previously reported for healthy pigs (Friendship et al., 1984; Schalm et al., 1986), confirming the non-infectious nature of the lameness.

Porcine serum haptoglobin concentrations increase following inflammatory processes, infections and surgery (Petersen et al., 2004). Clinical signs of lameness have been reported to be associated with high haptoglobin concentrations in slaughter pigs (Petersen et al., 2002a,b), but these studies also included pigs with infectious conditions, such as infectious arthritis. In the current study, concentrations did not differ between the lame and healthy control animals. The concentrations of haptoglobin in lame animals were consistent with previous studies (Petersen et al., 2002a; Heinonen et al., 2006). The haptoglobin concentrations in the healthy control animals were higher than values reported by Petersen et al. (2002a,b), but agreed well with the results obtained in a previous Finnish study (Heinonen et al., 2006). This may be due to differences in the laboratory methods used. The control animals in this study were selected from the same groups as the lame study animals to prevent the influence of other factors.

Undesirable side effects of ketoprofen are typical for non-selective NSAIDs, with gastrointestinal irritation being the most frequently found adverse effect (Veyes, 1991; Rainsford et al., 2003). The risk increases as the plasma concentration of the active ingredient increases. The ketoprofen peak plasma concentration was lower after oral administration than after IM administration at the same dose level (Raekallio et al., 2008). We estimated that plasma concentrations achieved after the higher dose used in present study were at similar levels as following the administration of 3 mg/kg IM. Although the medication period was longer than the approved duration, no adverse events were clinically observed.

Treatment proved to be more efficient on farms with solid concrete or partly slatted floors than on farms with fully slatted floors. The prevalence of lameness was greater among pigs housed on fully slatted floors than on solid floors (Jorgensen, 2003), but there have been no reported studies on the effect of floor type on treatment efficacy. Deep bedding decreased the risk of abnormal gait (Kilbride et al., 2009). Due to the limited number of animals in this study, no statistical analysis was performed to evaluate the influence of deep litter bedding on treatment success. However, providing a lame animal with a sufficient amount of bedding should improve the tolerance of pain and was therefore considered helpful as an adjunct to the use of analgesics in pain management (Short, 1998).

Conclusions

Non-infectious lameness of sows and gilts could be efficiently treated with oral ketoprofen at a dose of 2 mg/kg for five consecutive days.

Conflict of interest statement

Katja Mustonen was employed by Vetcare, the subsidiary of which is Provivo. During this study she was off duty and her work was supported by grants from the Mercedes Zachariasssen Foundation, the Orion-Farms Research Foundation and the Academy of Finland. The other authors of this paper have no financial or personal relationship with people or organisations that could inappropriately influence or bias the content of the paper.

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