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Clinical effects of buprenorphine on open field behaviour and gait symmetry in healthy and lame weaned piglets

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ABSTRACT

Lameness in pigs decreases animal welfare and economic profit for the farmer. An important reason for impaired welfare in lame animals is pain due to lameness. No direct measurement of pain is possible in animals, and methods to indirectly detect and quantify the amount of pain an animal is experiencing are urgently needed. In this study, two methods to assess pain associated with lameness in pigs were evaluated to determine if they were sensitive enough to detect a lameness reduction as an effect of an experimental analgesic medication. Asymmetry associated with lameness was objectively quantified using pressure mat kinetic parameters: peak vertical force (PVF), load rate (LR), vertical impulse (VI) and peak vertical pressure (PVP). Locomotor activity was assessed in an open field test. A dose of 0.04 mg/kg buprenorphine, a strong analgesic, was used to treat 10 lame pigs, while eight other lame pigs, treated with physiological saline solution, served as controls.

Buprenorphine decreased lameness-associated asymmetry for pressure mat LR ($P = 0.002$), VI ($P = 0.003$) and PVP ($P = 0.001$) and increased activity of the lame pigs in the open field ($P = 0.023$), while saline-treated animals did not show any changes in asymmetry and became less active in the open field ($P < 0.001$). It was concluded that measurement of gait asymmetry by pressure mat analysis and locomotor activity in an open field test are both sensitive enough to detect the analgesic effects of buprenorphine when used to treat moderate to severe clinical pain in a relatively small group of affected pigs. The methods used in this study may also provide promising additional tools for future research into early pain recognition and lameness treatment in pigs.

Introduction

Lameness is a common problem in pig husbandry and results in both a reduced animal welfare and economic losses to the farmer (Anil et al., 2009a; Kilbride et al., 2009; Jensen et al., 2012). The decreased animal welfare is due to pain, as well as a decreased ability to show normal behaviour (Anil et al., 2009b). It is important to detect and adequately treat these lamenesses, which are usually caused by painful processes. Lame pigs may also provide an interesting model for testing potentially analgesic treatments for use in humans.

To assess pain associated with lameness in pigs, objective and sensitive methods are required. Several methods to assess pain have been developed, mostly in rodents. Many of these methods focus on reflex testing of nociception (Di Giminiani et al., 2013; Tapper et al., 2013; Mohling et al., 2014). A drawback to testing nociception in this way is that it does not necessarily reflect the perception of pain by the animal (Mao, 2012; Cobos and Portillo-Salido, 2013), and there is a need for additional methods to indirectly quantify pain (Cobos and Portillo-Salido, 2013; Cobianchi et al., 2014).

In this study, we used two indirect methods to quantify pain. Firstly, we assessed locomotion asymmetry using kinetic parameters collected with a pressure mat. Pressure mat analysis of kinetic parameters is a useful tool to detect lameness in several species (Lequang et al., 2010; Oosterlinck et al., 2010a, 2010b, 2011; Maertens et al., 2011; Karriker et al., 2013). This method is especially useful for pigs, since it is possible to collect data on several footfalls in one run and thus to calculate asymmetry indices (ASIs) from one run. This minimises the effects of velocity on kinetics, which are difficult to control in these animals (Meijer et al., 2014a, 2014b).

Secondly, we quantified spontaneous locomotor activity in an open field test. Open field activity has been used extensively in rodents to measure spontaneous exploratory behaviour. It has also been used in pigs, for example to study the effect of head trauma, early isolation and various substances on exploratory activity (Fraser, 1974; Thodberg et al., 1999; Kanitz et al., 2004; Friess et al., 2007; van der Staay et al., 2009a).

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To help validate pressure mat analysis and the open field test for assessment of pain associated with lameness, we compared measurements from 18 clinically lame pigs treated with 0.04 mg/kg buprenorphine (a potent analgesic acting as a μ-opioid antagonist) and lame pigs treated with a placebo (physiological saline). Buprenorphine has been shown to be effective in pigs (Hermansen et al., 1986; Rodriguez et al., 2001) and evidence for unwanted behavioural side effects is limited to small increases in motor behaviour in response to a dose of 0.10 mg/kg buprenorphine IM (Hermansen et al., 1986). However, no changes in behaviour were reported by Harvey-Clark et al. (2000) when they compared 0.10 mg/kg buprenorphine IM with 25 and 50 μg/h transdermal fentanyl patches.

We hypothesised that, since pain is the most obvious reason for an animal to display lameness, the administration of an analgesic should, at least partially, restore symmetric gait, measured by the pressure mat. We also expected that lame pigs would show increased activity in the open field test after treatment with buprenorphine. Animals that experience pain tend to be less active (Weary et al., 2006) and lame sows spend more time lying down (Grégoire et al., 2013). The animal tries to avoid pain by putting less weight on the affected limb and is less motivated to walk around. Changes in locomotor activity in the open field test may therefore reflect changes in the amount of pain an animal experiences.

In a pilot study (see Appendix: Supplementary material) we did not find any significant influences of a dose of 0.04 mg/kg buprenorphine IM on any of the outcome parameters used in the present study; therefore, this dose was used in the current study.

Materials and methods

The study was reviewed and approved by the local ethical committee of Utrecht University (approval number 2012.III.05.04, date of approval 23 May 2012) and was conducted in accordance with the recommendations of EU directive 86/609/EEC. All effort was taken to minimise the number of animals used and their suffering.

Animals

Eighteen lame Topigs 20 × Tempo pigs were selected from a commercial farm by a veterinarian. Due to logistic reasons, the pigs were collected in five batches, each 2 weeks apart. Inclusion criteria were 3- to 10-week-old pigs, which were clinically lame in one limb, but were able to stand and walk unaided, were without any concurrent disease and were not treated with antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs) for at least 48 h prior to selection.

Housing

The pigs were housed at the research facility of Utrecht University in groups of three or four pigs in pens with sawdust-covered solid concrete floors measuring 153 cm × 256 cm. They were provided with 11 h of light per day (from 07:00 to 18:00 h) from both daylight and artificial lighting. The ambient temperature was 22–24 °C. All pigs had ad libitum access to food (Groeiporco, De Heus Animal Nutrition), water and toys (plastic balls and metal chains).

Treatment

The analgesic used was Buprecare Multidosis (AST Farma), containing 0.3 mg/mL buprenorphine hydrochloride. Physiological saline solution (9 g/L sodium chloride; Eurovet Animal Health) was used as the control compound. A researcher not involved in data collection assigned each animal randomly to either the treatment or control groups and prepared the syringes with either buprenorphine or saline solution in the same volumes. The two solutions could not be distinguished by the person administering them to the pigs.

Pigs were allowed to acclimatise for 24 h. At the start of the experiment, the complete set of measurements (clinical examination, weighing, visual scoring of gait, open field testing and pressure mat measurements) was performed. The next day (24 h later), the pigs received an IM injection of either 0.04 mg/kg buprenorphine or an equal volume of saline solution; 1.5 h after injection, the measurements were repeated. This meant that pre- and post-treatment measurements were taken at comparable times of the day.

Data collection

Firstly, data that could be collected without disturbing pigs were noted (breathing rate and skin colour). Then, visual scoring of gait according to the protocol of Main et al. (2000) was performed. Heart rate, rectal temperature, mucous membranes and lymph nodes were examined and body mass was measured. All examinations were performed by an experienced veterinarian.

Open field testing was performed in a pen (153 cm × 256 cm bordered by a 90 cm high wall) in a separate room. A video camera was mounted approximately 2.5 m above the pen. Each pig was transported to the pen using a cart and was placed in the open field where testing immediately began. After 5 min, the recording was stopped and the pig was removed from the pen. The pen was rinsed with clean tap water between each pig.

The pressure mat had an active sensor surface of 1.95 m × 0.32 m containing 16,384 sensors with a pressure range of 0.27–127 N/cm^2 and a sampling frequency of 126 Hz (RSscan International), as previously described by Meijer et al. (2014a). Pigs were guided to the holding area and, after 1 min, the door leading to the runway was opened. Exploratory behaviour combined with candy rewards encouraged the pigs to walk across the runway. Test runs were repeated for each pig until three runs met the selection criteria in which the pig walked along the runway at a consistent velocity, looking straight ahead and without stopping. Walking was confirmed from a duty factor (the percentage of the total gait cycle the foot has contact with the ground) > 0.5.

After data collection, the pigs were sedated with 2 mg/kg IM azaperone (Stresnil, Elanco Animal Health) and euthanased by intracardiac injection of 200 mg/kg pentobarbital (Euthanimal, Alfasan Diergeneesmiddelen). Gross pathological examinations were performed at the Department of Pathobiology of the Faculty of Veterinary Medicine, Utrecht University, with specific attention being paid to the affected limb.

Data analysis

Open field behaviour

Videos were scored by an observer using the purpose-built scoring program OBSERVE (van der Staay et al., 2009b). The screen was divided into 12 squares of equal size and a score was recorded each time the pig crossed a line. If any notable behaviour occurred (for example, rearing or jumping against pen wall), this was also registered. The total amount of line crossings in 5 min was used as an index for locomotor activity.

Pressure mat

For the pressure mat data, claw strikes from the three valid runs were manually assigned to left fore (LF), right fore (RF), left hind (LH) and right hind (RH) limbs. Four kinetic parameters were collected: peak vertical force (PVF, N), load rate (LR, N/s), vertical impulse (VI, N·s) and peak vertical pressure (PVP, N/cm^2). The total left-right asymmetry index (ASI) was calculated for each of these parameters using a formula modified from Oomen et al. (2012):

$$ASI = \frac{(LF+LH)-(RF+RH)}{0.5*[(LF+LH)+(RF+RH)]}*100$$

This formula yields a dimensionless ratio between left and right pressure mat parameters. An ASI of 0 indicates perfect symmetry; the extreme values of –200 or +200 indicate non-weight-bearing lameness on either the left or right side, respectively. Absolute ASI values were used for subsequent analysis. To assess the effect of treatment on the parameters, the differences between pre- and post-treatment (difASI for asymmetry indices and difOF for open field activity) were calculated.

Statistical analysis

Normality of data was assessed using Q–Q plots and Kolmogorov–Smirnov test. We assessed whether pre- and post-treatment levels of ASIs and open field activity differed between treatment groups using either a paired samples *t* test for normally distributed data or Wilcoxon's signed rank test for non-normally distributed data. We then checked if treatment influenced difOF and the difASI of kinetic parameters. An independent samples *t* test was used for normally distributed data and a Mann–Whitney *U* test for non-normally distributed data. All data were analysed using SPSS version 20.0 for Windows (IBM) and R version 3.1.0 (R Foundation for Statistical Computing) and are presented as means ± standard deviation (SD). Statistical significance was set at $P < 0.05$.

Results

The pigs weighed 10.9 ± 5.3 kg (mean ± SD). All of these pigs were lame, with a visual score ranging from 1 (abnormal stride length, movements no longer fluent) to 4 (may not place affected limb on floor); general clinical examination did not show any other abnormalities. The post-mortem findings are presented in Table 1; no pathology was found in unaffected limbs.