Effects of long-term use of the preferential COX-2 inhibitor meloxicam on growing pigs

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Meloxicam, a preferential COX-2 inhibitor, is a commonly used NSAID in pigs. Besides having potential side effects on the gastrointestinal tract, this type of drug might potentially affect osteogenesis and chondrogenesis, processes relevant to growing pigs. Therefore, the effects of long-term meloxicam treatment on growing pigs were studied. Twelve piglets (n=6 receiving daily meloxicam 0.4 mg/kg orally from 48 until 110 days of age; n=6 receiving only applesauce (vehicle control)) were subjected to visual and objective gait analysis by pressure plate measurements at several time points. Following euthanasia a complete postmortem examination was performed and samples of the talus and distal tibia, including the distal physis, were collected. Trabecular bone microarchitecture was analysed by microCT scanning, bone stiffness by compression testing and growth plate morphology using light microscopy. Animals were not lame and gait patterns did not differ between the groups. Pathological examination revealed no lesions compatible with known side effects of NSAIDs. Trabecular bone microarchitecture and growth plate morphology did not differ between the two groups. The findings of this in vivo study reduce concerns regarding the long-term use of meloxicam in young, growing piglets.

Introduction

In the pig industry, procedures generating pain, like castration and tail docking, are routinely performed.[1–3] Additionally, pain and inflammation are frequently related to lameness, which is a common clinical observation in rearing piglets and sows.[4 5] However, despite increased awareness and attention for welfare in food-producing animals, (knowledge of) pain management significantly lags behind compared with companion animals and horses.[6] Therefore, the beneficial effects of pain relief on clinical presentation and animal welfare, as well as on hidden financial costs such as decreased production[7 8] and premature culling,[8–11] may not be appreciated appropriately. Further factors likely contributing to the underuse of anti-inflammatory pain medication in the pig rearing industry are both the labour-intense burden of selective treatment and concerns about associated side effects.

In medical[12] and veterinary pain ladders, treatment with NSAIDs is a base step in relieving pain. A recent meta-analysis of effective pain treatment in piglets following surgical procedures early in life concluded that high heterogeneity in study designs precluded definitive recommendations, yet treatment with NSAIDs was the only intervention with proven efficacy.[13] The most commonly prescribed NSAID in pigs is meloxicam,[14 15] which is also marketed for use in several other domestic species as well as human beings. Previous studies of meloxicam administration in pigs have reported both COX-1 and more potent COX-2 inhibition.[16] In pigs, meloxicam is licensed for single use in a dose of 0.4 mg/kg given intramuscularly or orally with an option to repeat 24 hours later.[17] However, as in other species, longer usage may be necessary to treat more chronic conditions associated with pain and inflammation (eg, joint disease).

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Side effects of NSAID treatment on the gastrointestinal tract, renal papillae and on primary haemostasis are well known and have been reported in human beings[18 19] and animals,[20 21] especially after prolonged use. In pigs, the information on the use of meloxicam and possible side effects is limited.[22–24] Currently, COX-2 inhibition during bone fracture healing is under debate in human medicine as it could possibly lead to delayed fracture healing by reducing prostaglandin concentrations.[25–30] Given the similarities between the processes of fracture healing and endochondral ossification, COX-2 inhibition could also possibly negatively affect skeletal development, especially in a fast-growing animal such as the pig. Studies on the effect of NSAID-mediated COX-2 inhibition on cartilage and bone formation are thus far conflicting, reporting both negative[31 32] and neutral to positive effects.[33 34] Only one in vitro study used porcine cartilage explants and reported that meloxicam did not interfere with cartilage repair.[33] However, Welting and others[35] found that in growing rabbits the COX-2 inhibitor celecoxib negatively affected the hypertrophic zone of the growth plate. Specific information regarding the effect of COX-2 inhibition on bone development in growing piglets is lacking, but piglets have been used as a model to study the effects of prenatal, neonatal and perinatal glucocorticoid administration. Birth weight and growth rate were not affected, but glucocorticoid treatment in perinatal piglets negatively affected structural bone development and associated mechanical properties.[36] The lack of scientific information regarding the effects on bone and cartilage formation of meloxicam in growing pigs urges the in vivo assessment of the use of meloxicam in these animals.

In this study, which is part of a larger study assessing efficacy and possible side effects of prolonged daily administration of meloxicam to rearing pigs with experimentally induced mono-arthritis (J. J. Uilenreef, F. J. van der Staay, E. Meijer, unpublished observations), the authors focused on identifying possible clinically relevant effects of meloxicam administration on the locomotor system. Objective evaluation of the locomotion by pressure plate analysis, combined with postmortem microCT and bone compression testing, was used as outcome parameters. Additionally, the gastrointestinal and renal systems were assessed by (histo-)pathological examination. The authors hypothesised that long-term, daily treatment of piglets with meloxicam at the registered dose would result in an increased incidence of gastrointestinal side effects compared with the negative control group. Further, the authors anticipated adverse effects on chondrogenesis and osteogenesis, more in particular a decreased hypertrophic chondrocyte differentiation in the growth plate and inferior trabecular bone parameters such as lower bone volume fractions (BV/TV). The study aims at contributing to clinical decision-making in (growing) pigs with regard to the administration of meloxicam for anti-inflammatory and pain management under conditions requiring prolonged treatment.

Materials and methods

Animals and housing

The 12 pigs used for this study were a subset of a larger group of 40 Topigs 20 × Piétrain piglets from the breeding herd of the Utrecht University teaching farm used to study the efficacy of meloxicam for treatment of experimentally induced osteoarthritis by injection with mono-iodoacetate (J. J. Uilenreef, F. J. van der Staay, E. Meijer, unpublished observations), in which this subset served as controls (injected with saline as placebo). Piglets were group-housed and provided with a covered nest area and environmental enrichment (metal chains, balls, chewing sticks). The nest area had a roof that could be pulled up. Each nest area had two heating lamps and the floor was covered with a rubber mat and thick layer of straw. Transparent rubber flaps hung down from the front side of the roof to provide extra shelter during the first weeks. Piglets were housed according to litter (eight piglets per litter) to minimise aggression and fighting. Animals had ad libitum access to water from a drinking nipple, straw and commercial standard food (supplier: De Heus Voeders B.V., Ede, The Netherlands) for growing pigs. Starting at one week of age, all piglets were fed with 'Romelko nurse', followed by 'Romelko prevent 3' in the week before weaning. Subsequently, pigs were fed as recommended by the feed supplier using 'Prevent 5', Stimulans 6 and 'Vital Plus'. Information regarding ingredients relevant to bone development (calcium, phosphorus and vitamin D) and gastric ulceration (crude fibre) can be found in online supplementary table 1.

During the 20-day acclimatisation period and in the first two weeks of the experiment, pigs were weighed twice a week, thereafter once a week.

Experimental design

After the acclimatisation period, the animals in this study received an intra-articular injection with 0.25 ml sterile 0.9 per cent saline solution (B. Braun Melsungen AG, Germany) as a placebo treatment against the arthritis-induced animals (not included in this study), as pointed out above. For this, animals were lightly anaesthetised in a two-step procedure consisting of an intramuscular injection with dexmedetomidine (15 µg/kg, Dexdomitor 0.5 mg/ml, Orion Pharma, Finland; 10 ml) followed 15 minutes later by an intramuscular injection with ketamine (10 mg/kg, Narketan 100 mg/ml, Vétoquinol S.A., France; 10 ml) in combination with midazolam (0.5 mg/kg, Midazolam Actavis 5 mg/ml, Actavis Group PTC ehf., Iceland; 10 ml). After five minutes the animal was transported to a dedicated area for surgery. After aseptic preparation the left intercarpal joint was injected. Recovery of anaesthesia was accelerated by administration of atipamezole (0.5 mg/kg Atipam, 5 mg/kg, Eurovet Animal Health BV, Bladel, The Netherlands).

From day 1 (48 days of age) until the end of the study (110 days of age), half (n=6) of the animals received applesauce freshly spiked with meloxicam (0.4 mg/kg, Metacam 15 mg/ml oral suspension, Boehringer Ingelheim Vetmedica, Germany), the other half (n=6) only received untreated applesauce.

Gait analysis

Before each pressure plate measurement session, animals were visually checked to make sure all animals were sound. Video recordings, obtained 1 day before and 1, 3 and 28 days after left carpal intervention, were assessed by two experienced porcine veterinarians, blinded for intervention and treatment. If present, lameness was scored according to the protocol of Main and others.[4] Quantitative gait parameters were obtained by pressure plate measurements (Footscan, RSscan, Belgium) at 1 day before and 1, 3, 7, 14, 28 and 56 days after intra-articular injection using the same set-up as used before in piglets.[37 38] During the habituation period preceding gait analyses, piglets were trained to trot over the runway at a steady pace without stopping. Runs were considered valid if the pig moved in a straight line and looked straight ahead. Measurements were repeated until at least four valid runs were collected.

Footfalls were manually assigned to the corresponding limb using the manufacturer's software. Peak vertical force (PVF) and vertical impulse (VI) were extracted from the data for each limb and normalised for bodyweight. Asymmetry indices (ASI) comparing contralateral limbs within one run were calculated for both PVF and VI using the following formulas:

$$\text{Contralateral front limbs (CLF): } CLF = \frac{(LF - RF)}{0.5 * (LF + RF)} * 100$$

$$\text{Contralateral hindlimbs (CLH): } CLH = \frac{(LH - RH)}{0.5 * (LH + RH)} * 100$$

This yielded a dimensionless number between −200 (indicating that no weight was put on the left limb) and 200 (indicating that no weight was put on the right limb). An ASI of 0 meant that weight bearing was perfectly symmetrical.[39]

Euthanasia

Animals were sedated and general anaesthesia was induced in the same way as described for the intra-articular injections. When the animals had reached a sufficient anaesthetic depth, they were euthanased by intravenous injection of 50 ml of Pentobarbital (Euthanimal, Alfasan, Woerden, The Netherlands, 400 mg/ml).

Gross pathology, tissue sampling and histopathology

Following euthanasia a complete postmortem examination was performed, including opening of the carpal, tarsal, shoulder, knee and elbow joints. Samples of the stomach, duodenum, jejunum, ileum, caecum and colon and both kidneys were taken and fixated in 10 per cent neutral buffered formalin. All samples were paraffin embedded and 3-µm-thick sections were cut using a microtome. After haematoxylin and eosin (HE) staining, samples were evaluated under light microscopy (Olympus BX-45, Zoeterwoude, The Netherlands).

Four-millimetre-thick samples of the left talus and distal tibia were taken using a K430 band saw (Kolbe, Germany; blades Munkfors, Sweden). After fixation in paraformaldehyde (4 per cent), bone samples were decalcified in 10 per cent EDTA, which took between two and six weeks. Bone samples were paraffin embedded and 3-µm-thick samples were obtained and HE stained. Photographs of the distal growth plate of the tibia were taken and the thickness of the hypertrophic and proliferative zones was independently measured by two observers with Fiji for ImageJ V.2.0.0-rc-43/1.50e using the protocol of Welting and others.[35]

MicroCT imaging and tissue mechanics

Right tali were stored at −18°C before microCT imaging and subsequent tissue testing. After thawing, cylindrical trabecular bone samples (diameter 7.5 mm) were obtained from the lateral and medial part of the caput tali with a hollow drill. With a diamond blade saw the distal ends of the samples were cut just above the cartilage; proximally the samples were cut to a length of 10 mm, ensuring plane parallel ends. MicroCT imaging was performed using a µCT 80 scanner (Scanco Medical AG), equipped with an aluminium filter to reduce beam hardening effects. Scanning was performed in air at a spatial resolution of 37 µm (voltage of 70 kV; intensity (current) 114 µA). Based on the histograms and visual comparison of differently thresholded images with the original scans,[40] a global threshold of 212 per mille of the maximum grey value was chosen. From the segmented images, quantitative trabecular bone parameters were calculated using the Scanco Medical software. Bone volume fraction (BV/TV) was calculated as the number of bone voxels divided by the total number of voxels in the sample. Structural parameters (trabecular number Tb.N.; trabecular thickness Tb.Th. and trabecular separation Tb.Sp.) were calculated by a distance transformation method. The degree of anisotropy (DA) was based on the Mean Intercept Length fabric tensor and defined as the largest principal fabric value over the smallest one.

After scanning, the stiffness of the bone samples was determined by non-destructive compression. Before testing, metal endcaps were glued at both sides of the cylindrical bone samples to reduce end artefact effects.[41 42] Then, bone samples were preloaded four times with 20 N, followed by a gradual compression with a force of 200 N at a speed of 0.1 mm/min. As mechanical behaviour of all bone samples tested was still in the elastic range, experimental stiffness of the samples was

determined by calculating the slope of the force-displacement curve in the 100–200 N region with Matlab r2015 (MathWorks, Natick, USA).

Statistical analysis

Normality of the data distribution was checked both visually and using the Shapiro-Wilk test. Since the data were not normally distributed, differences between the meloxicam-treated and vehicle control group (no meloxicam) were assessed using the Mann-Whitney U test. Data were analysed using SPSS statistics V.22 (IBM) and R Statistical software V.3.1.2.[43] Meloxicam effects were tested with P set at <0.05 and a correction for multiple comparisons was performed according to the False Discovery Rate method of Benjamini and Hochberg.[44] Unless indicated otherwise, results are presented as mean±sd.

Effect sizes (ES) were retrieved as Cliff's delta.[45] The interpretation for the present work is the following:<0.11, very small or no effect; 0.11–0.28, small effect; 0.29–0.43, medium effect; and >0.43, large effect. Differences were considered relevant if a P value<0.05 was found and the effect size was medium or large.

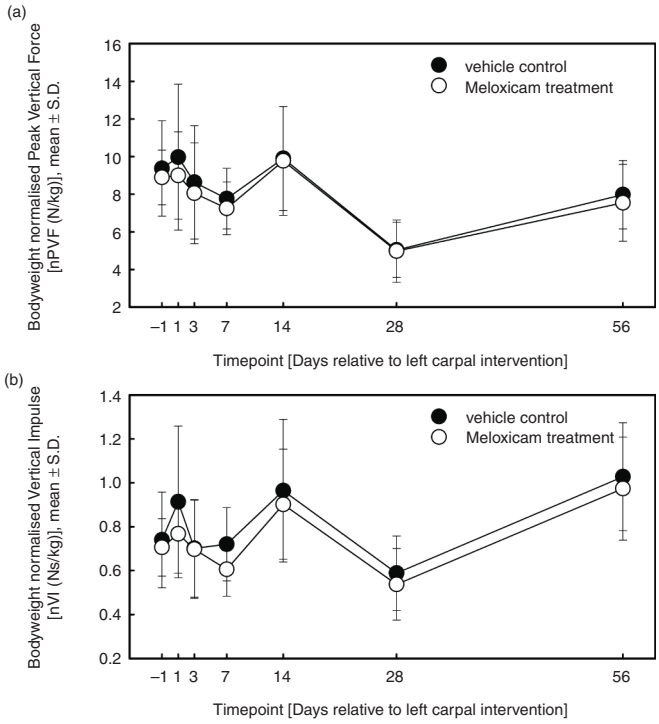

FIG 1: Mean (±sd) bodyweight normalised peak vertical force (nPVF N/kg) (a) and vertical impulse (nVI Ns/kg) (b) at the different time points for the vehicle control and meloxicam-treated animals

Results

The results of all statistical analyses and calculated effect sizes are listed in online supplementary table 2. Average weight of the pigs at the end of the study was 61 (±4.1) kg and did not differ between the two groups.

Gait analysis

No animals were considered lame before the pressure plate measurements and no gait abnormalities were observed on the video recordings. During the study period, average nPVF values fluctuated between 7 and 10 N/kg, but lower values were found in both groups on day 28 (Fig 1a). The same trend can be seen in the nVI, with average values between 0.7 and 1.0 Ns/kg and about 0.6 Ns/kg at week 28 (Fig 1b). No differences in bodyweight normalised, kinetic gait parameters were found between the meloxicam-treated and vehicle control animals.

Over time, ASI values fluctuated around 0, with a slight dip in both contralateral front limb PVF and VI on day 1 (Fig 2). No effects of NSAID treatment were found.

Histo(patho)logy

At postmortem examination, all pigs were normally developed and in good condition. Signs of mild enteritis were found in all animals, but in none of the animals, macroscopic or microscopic signs of gastric or enteric ulceration were encountered. Evaluation of the kidneys did not reveal renal papillary necrosis. In three pigs (all from the vehicle control group) 0.1–0.2-cm-sized (osteo-)chondral lesions were found at macroscopic evaluation of the tarsal joints. Microscopically, OC-associated lesions were found in five animals (two from the vehicle control group and three from the meloxicam-treated group). Two of these animals (meloxicam treated) showed two lesions on different locations within the tarsal joint.

Growth plate morphology

In both groups, the hypertrophic zone of the growth plate was thicker compared with the proliferative zone (ratio about 60:40). Meloxicam treatment did not affect the relative thickness of these zones (Fig 3).

Trabecular bone parameters are presented in Table 1. The differences observed between the meloxicam-treated and vehicle control animals were not statistically significant.

Discussion

This study did not show adverse side effects of long-term meloxicam usage in growing pigs on weight gain, gait, trabecular bone parameters, growth plate morphology, gastrointestinal integrity and kidney histology. These findings indicate that prolonged daily treatment with meloxicam at the licensed dose does not lead to detrimental side effects in growing pigs with regard to these body systems and their function. Based on the results of this study, meloxicam is a good candidate to consider for prolonged treatment of inflammation and pain, ultimately contributing to improvement of welfare in the pig industry.

None of the animals in this study was lame on subjective gait analysis; however, subtle changes may be missed when gait is only visually assessed.[46] Therefore, gait was objectively evaluated using a pressure mat sys-

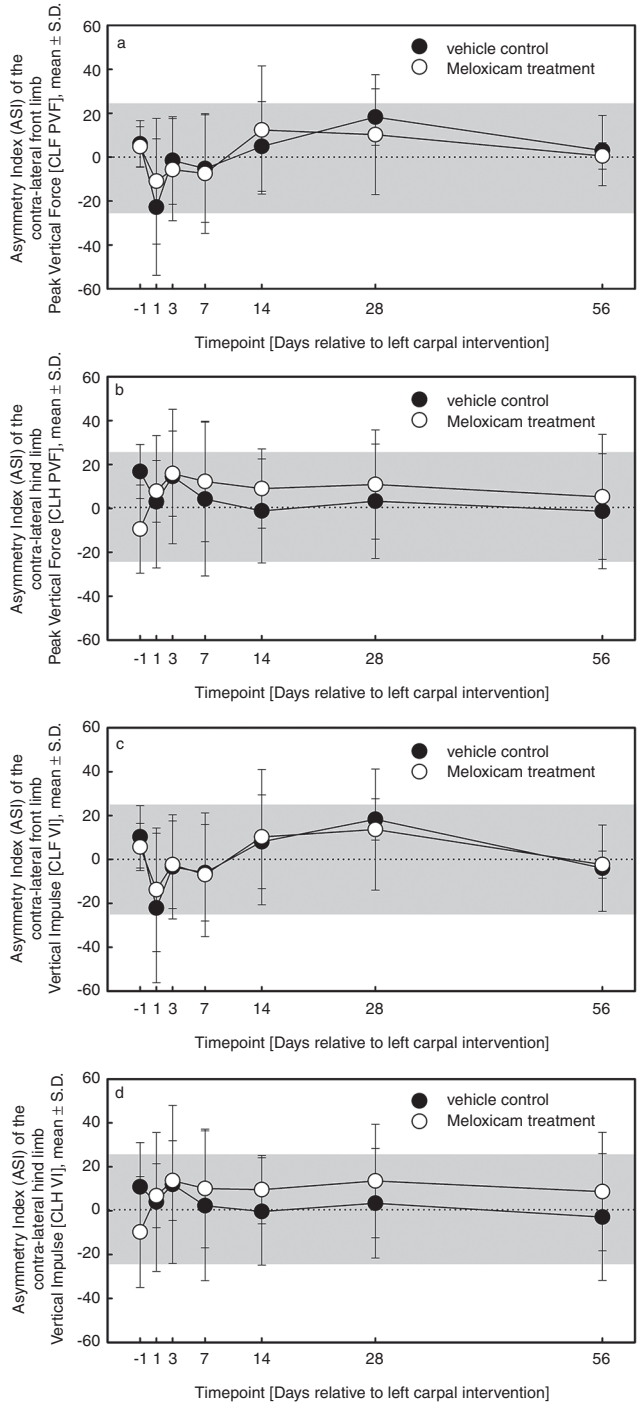

FIG 2: Asymmetry indices (ASI) comparing peak vertical force (PVF) of the left front limb and the right front limb (a). ASI comparing PVF of the left hindlimb and the right hindlimb (b). ASI comparing vertical impulse (VI) of the left front limb and the right front limb (c). ASI comparing VI of the left hindlimb and the right hindlimb (d). Mean values over time of the group that received NSAIDs and the group that did not receive NSAIDS are shown. CLF, asymmetry index of the contralateral front limbs; CLH, asymmetry index of the contralateral hindlimbs

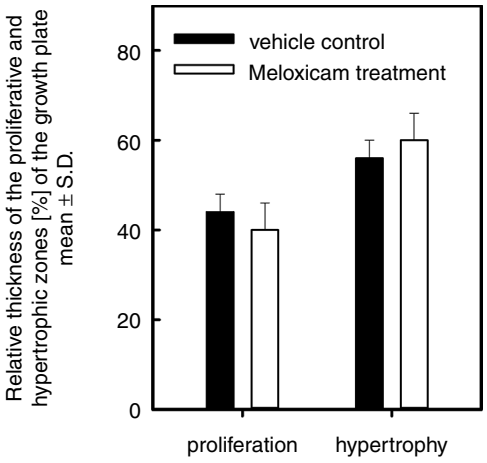

FIG 3: Relative thickness of the proliferative and hypertrophic zones respectively in the distal tibial growth plate for the meloxicam-treated and vehicle control animals

tem. No differences in bodyweight normalised kinetic gait parameters were found, indicating that limb loading was comparable between the meloxicam-treated and vehicle control animals.

Mean ASIs fluctuated around 0 and were comparable to values previously found in sound piglets.[37 38] In theory, healthy animals are expected to have perfect symmetry and thus ASIs of 0. In practice, perfect symmetry is almost never observed, neither in human beings nor in animals.[48–50] This normally occurring deviation from perfect symmetry is considered to be related to limb dominance. Functional differentiation of limbs and brain hemispheres may be responsible for this finding, resulting in small asymmetries in limb loading and other kinetic and spatiotemporal characteristics of gait.[51]

The 'dip' in front limb ASIs that was observed on day one was indicative of reduced loading of the left front limb. This may have been due to the intra-articular injection with saline. Although saline does not induce changes in cartilage, the increase in volume in the joint space may have stretched the articular capsule and may have caused some pain. This effect has been observed in human beings[52] and in horses,[53] although in horses the effect was only observable for two hours. Also in the hind leg ASI, a small but progressive change from decreased to increased weight bearing of the left hind leg was observed, which can also be explained by initial subtle weight shifting from the left to the right side in response to the slightly stretched joint capsule. Limb loading and mean ASIs did not differ between pigs that received meloxicam and pigs that did not. The authors therefore concluded that long-term administration of meloxicam to healthy pigs did not result in functional changes in locomotion and thus the locomotor apparatus.

In both groups, some small OC lesions were found, but incidence and severity of the lesions did not differ. Locomotion of pigs can be affected by the presence of OC lesions.[54] In growing foals, presence of radiographically visible OC lesions led to a temporary subclinical lameness, identified by a significant reduction of peak vertical force.[55] Nonetheless, in the present study no significant effects of the presence of OC lesions on gait kinetics were observed, possible due to the relatively small (microscopic) size of the lesions.

To the authors' knowledge, no in vivo studies about possible NSAID-associated side effects on bone and cartilage development in pigs have yet been published. Welting and others[35] reported negative

TABLE 1: Trabecular bone parameters of the lateral and medial part of the talus

Parameter	BV/TV[1]		Tb.N. (1/mm)		Tb.Th. (mm)		Tb.Sp. (mm)	
Metacam?	Yes	No	Yes	No	Yes	No	Yes	No
Average lateral part	0.39	0.37	2.53	2.58	0.16	0.15	0.35	0.34
SD lateral part	0.04	0.04	0.24	0.31	0.01	0.01	0.05	0.04
Average medial part	0.34	0.31	2.41	2.31	0.14	0.14	0.37	0.40
SD medial part	0.05	0.05	0.20	0.27	0.01	0.01	0.04	0.07

Parameter	DA[1]		Density (mg HA/cm³)		Stiffness (N/mm)	
Metacam?	Yes	No	Yes	No	Yes	No
Average lateral part	1.67	1.73	844.72	844.02	2165.2	1462.5
SD lateral part	0.09	0.08	13.87	12.85	405.5	247.1
Average medial part	1.91	1.92	849.89	849.59	1302.4	1377.4
SD medial part	0.21	0.20	12.44	11.28	468.1	564.0

BV/TV, bone volume fraction; DA, degree of anisotropy; Tb.N., trabecular number; Tb.Th., trabecular thickness; Tb.Sp. trabecular separation

effects of celecoxib treatment on the hypertrophic chondrocytes of the growth plate in rabbits. In contrast, the authors did not find any effects on bone and cartilage morphology. Although COX selectivity for celecoxib in rabbits is not established, in human beings celecoxib is much more selective for COX-2 than meloxicam.[56] Additionally, growth plate morphology of the pig is different compared with that of rabbits. In the pig, the hypertrophic zone of the growth plate is thickest, whereas the proliferative zone is the thickest in the rabbit. This might be explained by differences in (relative) growth rate, as has been shown in dogs.[57]

In the gastrointestinal system and kidneys, no lesions consistent with NSAID side effects were found. The authors did not expect to find renal changes as meloxicam is considered relatively safe for kidneys. Short-term usages in pigs did not show adverse effects[17] and in older cats, even when suffering from chronic kidney disease, long-term maintenance doses of meloxicam were considered safe.[58] The total absence of gastrointestinal ulcerations is somewhat surprising. In intensive farming, litters are mixed and housing conditions may not completely satisfy normal (rooting) behaviour. This may give rise to increased stress levels, associated with the development of gastrointestinal ulcerations.[59] Possibly, the fact that the authors used a very pig-friendly system in which they kept littermates together in an environment that was substantially more enriched compared with commercial housing may have either prevented formation of ulcers and/or the exacerbation of those by meloxicam. Furthermore, pigs had permanent access to straw, which has a protective effect on the gastric mucosa.[59–61] In the group of animals with induced arthritis, gastric and duodenal ulcerations were found, but the incidence and severity of the lesions were comparable between the meloxicam-treated and vehicle control group (J. J. Uilenreef, F. J. van der Staay, E. Meijer, unpublished observations). The effect of housing conditions on particularly the gastrointestinal side effects needs to be followed up in further research using commercial housing conditions.

There are several limitations to this study. The small sample size prohibits drawing firm conclusions. Furthermore, the current study did not aim at evaluating dose-response effects of meloxicam. Only prolonged oral administration at the licensed dose of 0.4 mg/ml once daily was investigated, representing the most likely conditions in practice under which meloxicam would be used. In piglets, the licensed dose has been reported to result in inadequate tissue levels to inhibit COX-2 to an extent sufficient for a good anti-inflammatory effect.[23] However, in that study the piglets were only aged two weeks. Increasing the dose is likely to result in a more potent anti-inflammatory effect, but may also produce more or stronger unwanted side effects.

Conclusion

The results of this in vivo study indicate that prolonged daily use of oral meloxicam at the licensed dose of 0.4 mg/kg did not lead to any of the thus far known NSAID-associated side effects in growing pigs. Given the high incidence of painful interventions and conditions in the modern pig-farming industry, this information may help veterinarians and farmers to decide to treat pigs that are in pain with a NSAID and may thus improve the welfare of pigs. Clinical decision-making with regard to administering or withholding NSAIDs because of possible side effects should not be made on in vitro data only, but should be backed up by subsequent in vivo validation in the target species.

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Competing interests None declared.

Ethics approval The study was reviewed and approved by the ethical committee of Utrecht University (no. 2014.I.11.085, date of approval December 17, 2014), The Netherlands, and was conducted in accordance with the recommendations of EU directive 86/609/EEC.

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