Effect of seven-day administration of carprofen or meloxicam on renal function in clinically healthy miniature pigs

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ABSTRACT: Carprofen or meloxicam are nonsteroidal anti-inflammatory drugs (NSAIDs), which may elicit a variety of renal disturbances. Prior to this study, the effects of carprofen or meloxicam on renal function in pigs were unknown. A total of 21 clinically healthy Goettingen miniature pigs (36.9 ± 7.22 kg) were divided into three groups based on what they were administered – carprofen, meloxicam or saline. First, blood was collected from the jugular vein and urine by ultrasound-guided cystocentesis. Serum urea (U) and creatinine (CR), fractional clearance of sodium (FCNa), urine gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) activities, urine protein/creatinine ratio (UP/UC), urine gamma-glutamyltransferase/creatinine ratio (GGT/CR) and urine alkaline phosphatase/creatinine ratio (ALP/CR) and urine analysis – urine specific gravity (USG) and sediment microscopy were assessed before and seven days after daily intramuscular administration (IM) of saline (1.5 ml per animal), carprofen (2 mg/kg) or meloxicam (0.1 mg/kg). All animals had identical housing, feeding and unlimited water intake and had not undergone surgery or been administered any medication for three months prior to this. All pigs served as control groups for an experimental study of fracture healing using transplantation of mesenchymal stem cells and scaffolds. The data were analyzed using a one way ANOVA and a Mann-Whitney test ($P < 0.05$). In pigs receiving carprofen, serum urea and creatinine were significantly decreased, compared to the control ($P < 0.01$) or meloxicam ($P < 0.05$) groups. In animals receiving meloxicam FCNa was significantly increased ($P < 0.05$) and urine specific gravity significantly decrease ($P < 0.05$) compared to the pretreatment values. Two carprofen-treated pigs had a slight increase in renal tubular epithelial cells upon urine sediment examination. Intramuscular administration of carprofen or meloxicam in healthy miniature pigs for seven days causes no clinically important changes in selected renal parameters (without azotemia). However these changes indicate mild damage of renal tubules. Despite these findings, meloxicam or carprofen are recommended for analgesia in healthy pigs.

Keywords: swine; non-steroidal anti-inflammatory drugs; renal safety

Most surgeries require high-quality analgesia. Due to damaged tissues, surgery often leads to inflammation (Lemke, 2004). In such cases anti-inflammatory analgesics are the best option. Non-steroidal antiinflammatory drugs (NSAIDs) are a good alternative to analgesia. Depending on the area of tissue damage and the duration of the painful process, NSAIDs must often be administered for long periods of time. In small animals (dogs and cats) carprofen and meloxicam are used for these purposes very often. There are many reports in the literature documenting both their adverse and beneficial effects (Curry et al., 2005; Luna et al., 2007). However, information regarding the application of meloxicam or carprofen in pigs is scant (Swindle, 2007).

Carprofen and meloxicam are NSAIDs whcih cause analgesia by suppressing the formation of prostaglandins through inhibition of cyclooxygenase 1 and 2 (COX-1 and COX-2). Prostanoids

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generated by COX-2 play an important role in inflammatory and painful reactions to tissue damage (Ferreira, 2002; McCrory and Lindahl, 2002). Apart from their positive effects, NSAIDs may also have numerous negative effects, impairment of kidney function being among the most severe. Hypotension and/or anesthesia during surgery leads to increased tonus of the sympathetic nervous system, resulting in prostaglandin-dependent changes in renal blood flow (Dunn and Zambraski, 1980). NSAID-induced inhibition of prostaglandins production may have a negative influence on renal hemodynamics and glomerular filtration rate with subsequent renal disorder (Oliver et al., 1981, 1983; Zambraski, 1995). Prostaglandins with a protective impact on the kidney are primarily based on the effectiveness of COX-1. If the kidney is in a prostaglandin-dependent condition, weaker adverse effects on renal hemodynamics are anticipated after application of meloxicam or carprofen compared to other NSAIDs. COX-2 also plays a major role in physiological kidney function (Harris, 2000). Carprofen and meloxicam are NSAIDs that preferentially inhibit COX-2, but partially also affect COX-1 (Kay-Mugford et al., 2000) with potential renal risks.

NSAIDs may cause numerous renal disorders, including acute renal failure (ARF), chronic renal failure (CRF), nephrotic syndrome, interstitial nephritis, water metabolism abnormalities, sodium retention and hypercalcemia (Clive and Stoff, 1984). However, studies on the effects of NSAIDs on renal function in anesthetized dogs after a single-dose administration of carprofen or meloxicam (Crandelli et al., 2004) did not show any clinically significant alteration in renal parameters. Similarly, a study by Lobetti and Joubert (2000) investigating the influence of NSAIDs on renal function in anesthetized dogs did not detect adverse effects after administration of carprofen. Information on the effects of carprofen or meloxicam on the renal function of pigs is still missing. Junot et al. (2008) describe the influence of meloxicam on the renal function of piglets. While meloxicam was applied only once during the general anesthesia no deviations from monitored parameters were observed (urinary flow – UF, glomerular filtration rate – GFR and renal blood flow – RBF) after administration of meloxicam compared to the control group.

Patient renal function can be monitored by laboratory tests of blood and urine. Biochemical tests include blood urea (U), creatinine (CR), fractional clearance of sodium (FCNa), urine gamma-glutamytransferase (GGT) and alkaline phosphatase (ALP) activities, urine protein/creatinine ratio (UP/UC), urine gamma-glutamyltransferase/creatinine ratio (GGT/CR) and urine alkaline phosphatase/creatinine ratio (ALP/CR) which report on glomerular filtration and renal failure. Urine analysis includes urine specific gravity (USG) and sediment microscopy with a focus on renal tubular epithelial (RTE) cells, which are informative with regard to renal tubular damage. Increases in the above-mentioned parameters (except USG) indicate possible renal failure (Osborne et al., 1995).

The purpose of this study was to compare the effect of administration of carprofen and meloxicam in miniature pigs on selected serum and urine parameters that might indicate impaired renal function. Both above-mentioned NSAIDs were, in contrast to previous studies, administered for a relatively long time (one week), which should outline the possibilities for prolonged NSAID therapy in miniature pigs. Thus, this analgesia could be used not only for orthopedic surgery in miniature pigs, but also for other surgical procedures carried out on these animals.

MATERIAL AND METHODS

Study group of animals

Twenty-one clinically healthy Goettingen miniature pigs – females weighing 36.9 ± 7.22 kg (mean ± SD) and aged 2.3 ± 0.62 years were used for the study. All animals were clinically normal, had identical housing, feeding and unlimited water intake and were free from medication or surgical procedures for the three months prior to the commencement of experiments. All pigs served as control groups for an experimental study (NPV II Research Project 2B06130) on fracture healing using transplantation of mesenchymal stem cells (MSCs) and scaffolds, segmental bone defect stabilized by locking compression plate without MSC transplantation. All procedures were carried out with consent of the Ethical Committee (No. 46613/2003-1020) of the University of Veterinary and Pharmaceutical Sciences.

Treatment groups and drug administration

The pigs were divided into three treatment groups: group CAR – carprofen 2 mg/kg *i.m.* (Rimadyl; Vericore Ltd.), group MEL – meloxicam 0.1 mg/kg

i.m. (Metacam; Labiana Pharm.) and group CON – saline 0.9% 1.5 ml *i.m.* per animal (control). Each pig received drugs intramuscularly once a day for seven days in the above-mentioned doses. Blood and urine sample collection in all pigs were carried out before beginning with drug administration (T0) and seven days after daily drug administration. All drugs were applied daily at 2:00 p.m., samples were collected at 1:00 p.m.

Data collection

Blood was collected by venipucture from *v. cava cranialis*. Urine samples were collected aseptically by ultrasound-guided cystocenthesis. Urine and blood samples were collected before (T0) and seven days after medication (CAR, MEL, CON).

Serum blood variables evaluated included serum urea (U) and serum creatinine (CR). Urine variables evaluated included fractional clearance of sodium (FCNa), urine gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) activities, urine protein/creatinine ratio (UP/UC), urine gamma-glutamyltransferase/creatinine ratio (GGT/CR) and urine alkaline phosphatase/creatinine ratio (ALP/CR). Microscopic evaluation of the urine (performed by one investigator) was done on urine sediment stained with the Sternheimer-Malbin stain which enabled the differentiation of renal tubular epithelial (RTE) cells from other urinary epithelial cells (Osborne et al., 1995). The finding of RTE cells in the urine was subjectively scored on a scale of one to four. A score of one represented one RTE cell/two to three high power fields (HPF; 400× magnification), two represented 1–2 RTE cells/HPF, three represented 2–4 RTE cells/HPF, and four represented more than five RTE cells/HPF (Vaden et al., 2009).

Statistical analyses

At first, variables of each group of animals seven days after medication were compared with variables of the group before medication – at time T0 (CAR vs. T0, MEL vs. T0, CON vs. T0). Thereafter, variables evaluated seven days after medication were compared with each other (CAR vs. MEL, CAR vs. CON, MEL vs. CON). All variables were compared by means of one way ANOVA and the Mann-Whitney test. In all analyses, a value of $P < 0.05$ was considered significant.

RESULTS

In pigs receiving carprofen, serum urea and serum creatinine were significantly decreased compared to the control ($P < 0.01$) or meloxicam ($P < 0.05$) groups (Figures 1 and 2).

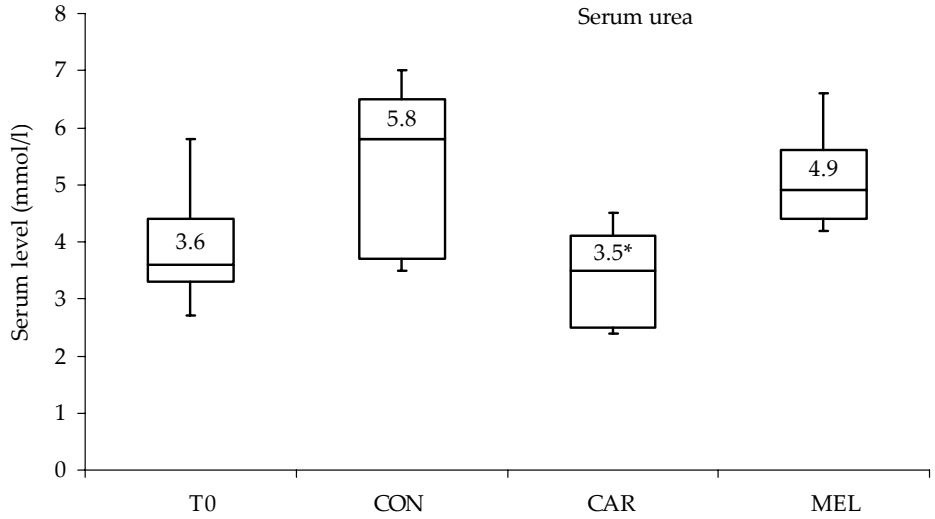

Figure 1. Box plot showing median (line, value), 25th–75th percentile (box) and nonoutlier maximum and minimum levels of serum urea in examined groups of pigs

T0 = before medication, CON = after administration of saline, CAR = after administration of carprofen, MEL = after administration of meloxicam

*significant decrease compared to the control ($P < 0.01$) or meloxicam ($P < 0.05$) groups

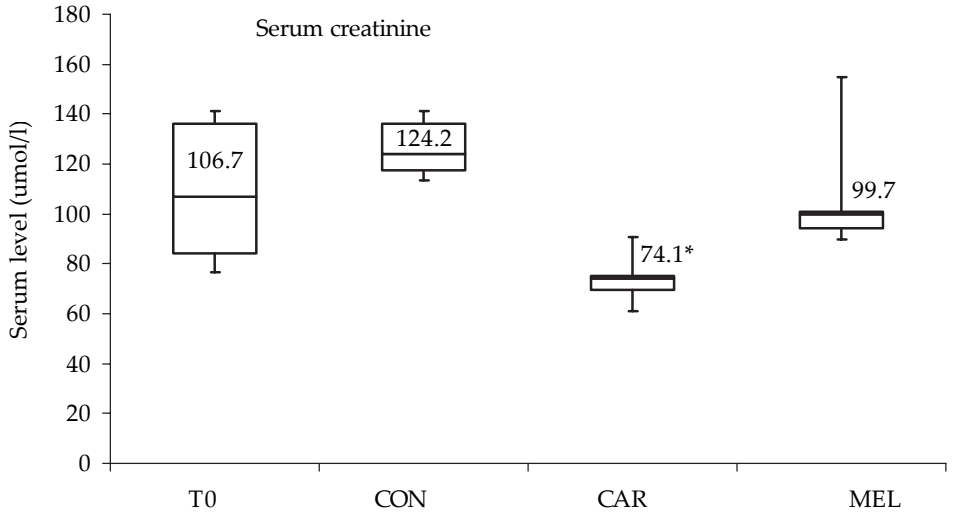

Figure 2. Box plot showing median (line, value), 25th–75th percentile (box) and nonoutlier maximum and minimum levels of serum creatinine in examined groups of pigs

T0 = before medication, CON = after administration of saline, CAR = after administration of carprofen, MEL = after administration of meloxicam
*significant decrease compared to the control ($P < 0.01$) or meloxicam ($P < 0.05$) groups

In pigs receiving meloxicam FCNa was significantly increased ($P < 0.05$) (Figure 3) and USG significantly decreased ($P < 0.05$) (Figure 4) compared to the pre-treatment values.

Two carprofen-treated pigs had a slight increase (scale 1) in RTE cells upon urine sediment examination compared to other groups including pretreatment values.

There were no changes in urine enzyme (GGT, ALP) activity and urine GGT/CR and ALP/CR ratio as an indicator of renal dysfunction. All animals were without azotemia.

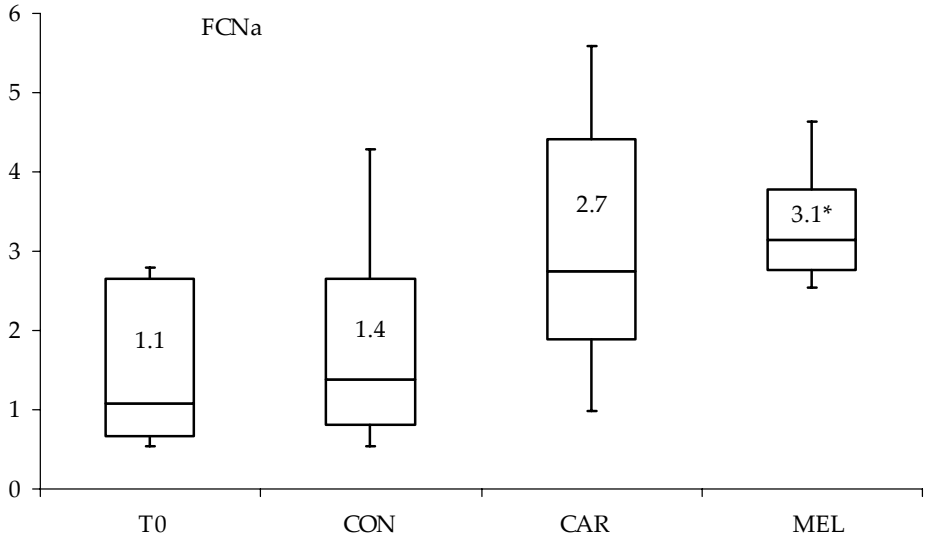

Figure 3. Box plot showing median (line, value), 25th–75th percentile (box) and nonoutlier maximum and minimum levels of fractional clearance of sodium (FCNa) in examined groups of pigs

T0 = before medication, CON = after administration of saline, CAR = after administration of carprofen, MEL = after administration of meloxicam
*significant increase ($P < 0.05$) compared to the pretreatment values

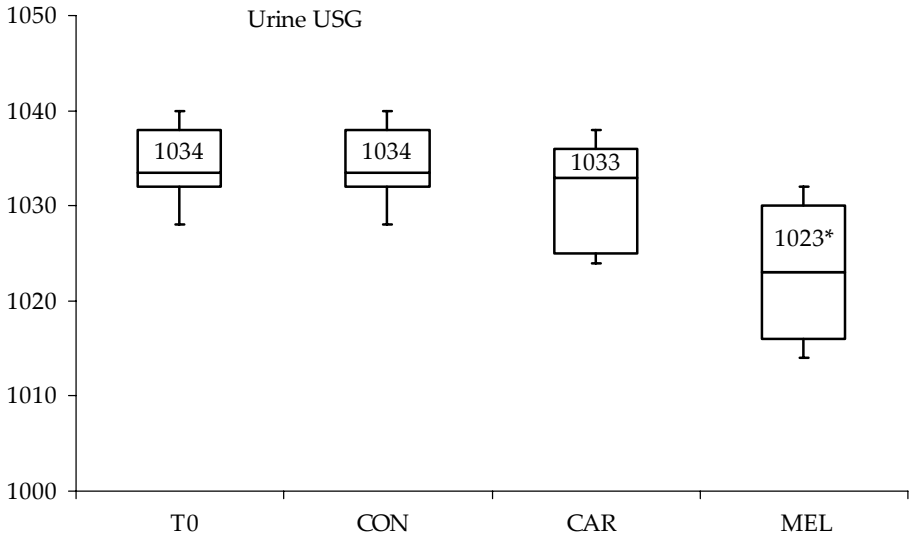

Figure 4. Box plot showing median (line, value), 25th–75th percentile (box) and nonoutlier maximum and minimum levels of urine specific gravity (USG) in examined groups of pigs

T0 = before medication, CON = after administration of saline, CAR = after administration of carprofen, MEL = after administration of meloxicam
*significant decrease ($P < 0.05$) compared to the pretreatment values

DISCUSSION

To assess the effects of long-term administration of NSAID, it was first necessary to determine the suitable dosage for pigs, which had not been described previously in the literature.

For meloxicam, many authors mention only single-administration doses. Fosse et al. (2008) report a single dose of 0.4 mg/kg administered intravenously (*i.v.*) for the pharmacokinetic and pharmacodynamic study of meloxicam in piglets. The same single dose of meloxicam in adult pigs was used by Swindle (2007) and Friton et al. (2006) in endotoxemia therapy and by Hirsch et al. (2003) in mastitis-metritis-agalactia syndrome therapy. A similar dosage (0.3 mg/kg) was administered by Girod et al. (2000, 2002) in their studies on the antiemetic effects of meloxicam. However, Reyes et al. (2002), used meloxicam in their neurological surgeries in piglets intravenously at the much higher dose of 1 mg/kg. Junot et al. (2008) applied meloxicam at a dose of 0.2 mg/kg when comparing its adverse effects to ketoprofen. Since the latter dose is close to the meloxicam dosage for dogs and cats (Mathews, 1997; Lascelles, 2000), we chose 0.1 mg/kg for week-long repeated administration of meloxicam dose.

Carprofen is often used in animals such as dogs, cats or horses (Mathews, 1997; Lascelles 2000). However, only Swindle (2007) reports on its use with regard to analgesia in pigs. He reported the dose of 2–4 mg/kg subcutaneously (s.c.), but does not mention the possibility of repeated administration. For the week-long repeated administration of carprofen in pigs we therefore chose the lower dose limit – 2 mg/kg. Crandelli et al. (2004) compared the effect of carprofen and meloxicam on renal function in dogs. They did not observe major deviations of selected parameters (GFR, U, CR) when comparing control and medicated groups. However, both substances were applied in single doses. We did not note any increase in pig serum U or CR in our study after a week-long medication with meloxicam or carprofen either. In pigs medicated with meloxicam we observed increased FCNa, which suggests possible alterations in renal tubular function (Osborne et al., 1995). However, the anticipated azotemia was not observed in animals with meloxicam or carprofen medication.

We believe that azotemia did not develop because we administered only a low dose of meloxicam (0.1 mg/kg) even though it was administered repeatedly. After a single application of meloxicam in piglets during anesthesia, Junot et al. (2008) found only mild changes in UF, GFR and RBF. Blood and urine parameters, however, were not recorded.

The above-mentioned changes observed by Junot et al. (2008), though statistically insignificant, partially correspond with our results. In pigs medicated with meloxicam we noted a significant increase in FCNa and decrease in urine USG. The lower urine USG values in pigs could be caused by sub-clinical renal damage or other non-kidney related diseases (Vaden et al., 2009). Lower urine USG could be also associated with limited secretion of antidiuretic hormone (ADH; Greene and Grauer, 2007). The higher values for the urine GGT/CR ratio may also indicate functional renal disorder after meloxicam application. This increase, however, was not statistically significant. An increased GGT/CR ratio could be caused by decreased GFR or severe glomerular damage (Vaden et al., 2009).

The creatinine and urea blood levels were within limits in the group of animals medicated with meloxicam. Azotemia occurs only after 75% damage of renal parenchyma (Osborne et al., 1995). Physiological limits of urea and creatinine values are not specific to renal damage. Levels of blood urea and creatinine in animals were lower in carprofen-medicated animals. Together these two parameters can be regarded as markers of glomerular filtration (Osborne et al., 1995). We may therefore speculate about increased glomerular renal filtration after carprofen medication, but we were not able to find or explain its cause. Ko et al. (2000) compared blood urea nitrogen (BUN, BUN × 2.14 = U) and creatinine values in dogs. They did not find any deviations from our values measured in pigs. This may be due to the different impact of carprofen on U and CR in dogs and pigs in relation to medication with carprofen. Unfortunately, a more comprehensive explanation or references are not available. The presence of RTE cells in the urine sediment indicates transitional renal damage. RTE cells are excreted into urine during normal exchange or as a result of renal damage (Lobetti and Joubert, 2000). In our groups of pigs we observed a statistically insignificant occurrence of RTE cells only in two animals medicated with carprofen, with no other abnormalities in the observed parameters. In animals medicated with meloxicam in which we observed increased FCNa and decreased urine USG indicating possible renal damage, RTE cells were not found in a single animal. For further assessment of renal function, some additional tests would be helpful. Nevertheless, as the animals were stabled in groups, we could not check individually water intake and urine production. Moreover, the experiments were carried out with limited laboratory equipment.

CONCLUSION

Intramuscular administration of carprofen or meloxicam in healthy miniature pigs for seven days causes no clinically important changes in selected renal parameters (without azotemia). However, these changes, especially in pigs after administration of meloxicam, could indicate mild damage of renal tubules. Despite the findings, meloxicam or carprofen at the described dosages is recommended for analgesia in healthy miniature pigs.

This type of NSAID medication seems to be suitable not only in miniature pigs used as fracture healing models in our research, but also on these animals in relation to other surgical procedures.

REFERENCES

Clive DM, Stoff JS (1984): Renal syndromes associated with nonsteroidal anti-inflammatory drugs. New England Journal of Medicine 310, 563–572.

Crandelli DE, Mathews KA, Dyson DH (2004): Effects of meloxicam and carprofen on renal function when administered to healthy dogs prior to anesthesia and painful stimulation. American Journal of Veterinary Research 65, 1384–1390.

Curry SL, Cogar SM, Cook JL (2005): Nonsteroidal antiinflammatory drugs: a review. Journal of American Animal Hospital Association 41, 298–309.

Dunn MJ, Zambraski EJ (1980): Renal effects of drugs that inhibit prostaglandin synthesis. Kidney International 18, 609–622.

Ferreira SH (2002): Peripheral analgesic sites of action of antiinflammatory drugs. International Journal of Clinical Practice 7 (Suppl.), 2–10.

Fosse TK, Haga HA, Hormazabal V, Haugejorden G, Horsberg TE, Ranheim B (2008): Pharmacokinetics and pharmacodynamics of meloxicam in piglets. Journal of Veterinary Pharmacology and Therapeutics 31, 246–252.

Friton GM, Schmidt H, Schroedl W (2006): Clinical and anti-inflammatory effects of treating endotoxin-challenged pigs with meloxicam. Veterinary Record 159, 552–557.

Girod V, Bouvier M, Grelot L (2000): Characterization of lipopolysaccharide-induced emesis in conscious piglets: effects of cervical vagotomy, cyclooxygenase

inhibitors and a 5-HT(3) receptor antagonist.. Neuropharmacology 39, 2329–2335.

Girod V, Dapzol J, Bouvier M, Grelot L (2002): The COX inhibitors indomethacin and meloxicam exhibit antiemetic activity against cisplatin-induced emesis in piglets. Neuropharmacology 42, 428–436.

Greene SA, Grauer GF (2007): Renal disease. In: Tranquilli WJ, Thurman JC, Grimm KA (eds.): Lumb and Jones' Veterinary Anaesthesia and Analgesia. 4th ed. Blackwel Publishing, Ames, Iowa. 915–919.

Harris RC (2000): Cyclooxygenase-2 in the kidney. Journal of the American Society of Nephrology 11, 2387–2394.

Hirsch AC, Philipp H, Kleemann R (2003): Investigation on the efficacy of meloxicam in sows with mastitis-metritis-agalactia syndrome. Journal of Veterinary Pharmacology and Therapeutics 26, 355–360.

Junot S, Troncy E, Keroack S, Gauvin D, del Castillo JR, Boivin R, Bonnet JM (2008): Renal effect of meloxicam versus ketoprofen in anaesthetized pseudo-normovolaemic piglets. Canadian Journal of Physiology and Pharmacology 86, 55–63.

Kay-Mugford P, Benn SJ, LaMarre J, Conton P (2000): In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. American Journal of Veterinary Research 61, 802–810.

Ko JC, Miyabiyashi T, Mandsager RE, Heaton-Jones TG, Mauragis DF (2000): Renal effects of carprofen administered to healthy dogs anesthetized with propofol and isoflurane. Journal of American Veterinary Medical Association 217, 346–349.

Lascelles DX (2000): Clinical pharmacology of analgesic agents. In: Hellebrekers LJ (ed.): Animal Pain. Van der Wees, Utrecht. 85–116.

Lemke KA (2004): Understanding the patophysiology of perioperative pain. Canadian Veterinary Journal 45, 475–480.

Lobetti RG, Joubert KE (2000): Effect of administration of nonsteroidal anti-inflammatory drugs before surgery on renal function in clinically normal dogs. American Journal of Veterinary Research 61, 1501–1507.

Luna SP, Basilio AC, Steagall PV, Machado LP, Moutinho FQ, Takahira RK, Brandao CV (2007): Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. American Journal of Veterinary Research 68, 258–264.

Mathews KA (1997): Non-steroidal antiinflammatory analgesics for acute pain management in dogs and cats. Veterinary and Comparative Orthopaedics and Traumatology 10, 122–129.

McCrory CR, Lindahl SG (2002): Cyclooxygenase inhibition for postoperative analgesia. Anesthesia and Analgesia 95, 169–176.

Oliver JA, Sciacca RR, Pinto J, Cannon PJ (1981): Participation of the prostaglandins in the control of renal blood flow during acute reduction of cardiac output in the dog. Journal of Clinical Investigation 67, 229–237.

Oliver JA, Sciacca RR, Cannon PJ (1983): Renal vasodilation by converting enzyme inhibition. Role of renal prostaglandins. Hypertension 5, 166–171.

Osborne CA, Stevens JB, Lulich JP, Ulrich LK, Bird KA, Koehler LA, Swanson LL (1995): A clinician's analysis of urinalysis. In: Osborne CA, Finco DR (eds.): Canine and Feline Nephrology and Urology, Williams and Wilkins, Baltimore. 136–205.

Reyes L, Tinworth KD, Li KM, Yau DF, Waters KA (2002): Observer-blinded comparison of two nonopioid analgesics for postoperative pain in piglets. Pharmacology, Biochemistry and Behavior 73, 521–528.

Swindle MM (2007): Swine in the laboratory. Surgery, Anesthesia, Imaging, and Experimental Techniques. 2nd ed. CRC Press, Boca Raton. 35–79.

Vaden SL, Knoll JS, Smith FWK, Tilley J (eds.)(2009): Blackwell's Five-Minutes Veterinary Consult: Laboratory Tests and Diagnostic Procedures: Canine and Feline. Wiley-Blackwell, Ames, Iowa. 763 pp.

Zambraski EJ (1995): The effects of nonsteroidal anti-inflammatory drugs on renal function: experimental studies in animals. Seminars in Nephrology 15, 205–213.

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