VETERINARY EVIDENCE
brought to you by RCVS KNOWLEDGE

Comparison of 0.2 Mg/kg Vs. 1.0 Mg/kg of Oral Meloxicam for Safe and Effective Analgesia in Domestic Rabbits

A Knowledge Summary by

Katherine Nield DVM Student [1*]
Merran Govendir BVSc, PhD, MEd, MANZCVSc, FHERDSA[1]

[1] Sydney School of Veterinary Science, The University of Sydney, Australia
[*] Corresponding Author (knie4444@uni.sydney.edu.au)

ISSN: 2396-9776
Published: 21 Jun 2019
in: Vol 4, Issue 2
DOI: http://dx.doi.org/10.18849/ve.v4i2.215
Reviewed by: Laura Dixon (PhD, BSc) and Valentin Parmen (BA, DVM, MRCVS)
Next Review Date: 11 August 2020

KNOWLEDGE SUMMARY

PICO question

In domestic rabbits, how does 1 mg/kg of oral meloxicam compare with 0.2 mg/kg of oral meloxicam for significant changes in pain behaviour, and kidney and liver biochemical analytes?

Clinical bottom line

Based on current available evidence, oral meloxicam at a dosage of 0.2 mg/kg daily when used as the sole analgesic does not provide adequate pain relief in rabbits. A dosage of 1 mg/kg daily is more efficacious, but it is unclear whether this is sufficient for postoperative pain management. The literature supports the safety of meloxicam at both 0.2 mg/kg and 1 mg/kg daily for healthy rabbits, based on liver and kidney biochemical analytes.

Five studies have been reviewed, which are a mix of randomised controlled trials and prospective clinical trials.

Clinical Scenario

There are an increasing number of rabbits being kept as pets, and owners are becoming more willing to pay for procedures such as surgery[1]. To ensure the rabbits entering your care receive the best treatment available, you decide to create an analgesic protocol for your clinic. Your research indicates meloxicam is the analgesic of choice, as it has a reduced risk of gut stasis in comparison with opioids[10-12], which is a life-threatening complication in rabbits[13]. Additionally, meloxicam has a palatable oral form for easy administration. However, you have heard that the minimum suggested dose of 0.2 mg/kg may not provide adequate analgesia[14], and you are unsure if the higher dose of 1 mg/kg would be a safe standard protocol[14]. You decide to conduct further research.

The evidence

The studies in this review are randomised controlled trials and prospective clinical trials, which are strong types of study designs[15]. However, the available studies selected small treatment groups and sample sizes with no statistical justification, weakening the statistical power of the evidence[16]. The prospective clinical trials do not demonstrate safety for postoperative or sick rabbits, reducing the generalisability of the data. The randomised controlled trials applied their analgesic protocols for only 2 to 3 days, so give limited data. In this review, conclusions about safety at each dose are drawn from four of the articles[4-7], and conclusions about analgesic efficacy are drawn from two of the articles[7, 8]. The findings in the articles are consistent. It is concluded that for both doses there is moderate evidence for the safety of meloxicam in healthy rabbits, due to the reproducibility of the safety data across studies. There is weak evidence for the analgesic efficacy for both dose rates, due to the limited behavioural data and inconclusive results.

Summary of the evidence

Fredholm et al. (2013)[6] *Prospective clinical trials addressing liver and kidney biochemical analytes*	
Population:	Eight-month-old (sexually mature), healthy New Zealand white rabbits (*Oryctolagus*

	cuniculus) of unstated gender, all from the same commercial source, bred to be free from *Pasteurella* spp. and weighing 2.41–2.89 kg.
Sample size:	Six rabbits
Intervention details:	• The sample size was not split into groups. • The subjects were habituated to the environment and handling for 5 days before commencement of the study. • Single dose study: All subjects were administered a single dose of 1 mg/kg of meloxicam orally via a 3 ml syringe, with blood collected immediately before the dose and then 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 36 hours after the dose. • After the final blood collection, this was followed by a 10 day wash out period. • Multi-dose study: All subjects were then administered 1 mg/kg of meloxicam solution orally via a 3 ml syringe every 24 hours for 5 days. Blood was collected immediately before and four hours after the dose on days 1 to 4. Blood was collected immediately before the dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 36 hours after the dose on day 5.
Study design:	Prospective clinical trial
Outcome studied:	• Plasma concentrations of meloxicam were measured in the blood samples from every collection using high pressure liquid chromatography (HPLC) and triple quadrupole mass spectrometry (MS). The samples at each concentration were validated (accuracy and coefficient of variation values stated within paper). Pharmacokinetic indices were determined via non-compartmental analysis through software. • Plasma biochemistry was analysed in the first blood sample (before the single dose meloxicam treatment) and the final blood sample (36 hours after the final multi-dose treatment). This measuring glucose, blood urea nitrogen (BUN), total protein, albumin, globulin, total calcium, phosphorus, sodium, potassium, chloride, bicarbonate, and total bilirubin concentrations. Creatine kinase (CK), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities were also measured. • Behaviour, attitude, mentation, amount of activity, food and water consumption, and faecal output were monitored (methods not stated).
Main findings: (relevant to PICO question):	• There was a significant increase ($P < 0.05$) in plasma BUN concentrations ($P = 0.01$), and ALP activities ($P = 0.018$), 36 hours after the final meloxicam treatment on day 5. Plasma BUN was within the normal reference range before and after treatment, and ALP activities were outside of the normal reference range before and after treatment. The authors suggested that this, in combination with the lack of change in other liver values, indicate the increases were not due to experimental factors. • There were no significant differences in other plasma biochemical values post-treatment. • Mean peak plasma concentration of meloxicam at 1 mg/kg after a single dose was 0.83 ug/ml, and after 5 days of dosing was 1.33 ug/ml. • Plasma concentrations of meloxicam considered therapeutic in dogs (0.82 ug/ml[17]) and humans (0.92 ug/ml for a single dose, 1.94 ug/ml after 5 days of dosing[18]) were achieved in rabbits through a dose rate of 1 mg/kg. • The accumulation of meloxicam in the plasma was higher than expected, with the amount of accumulation varying between subjects. • Average elimination half-life of meloxicam was approximately 6 hours for the single dose, and approximately 7 hours after 5 days of dosing.

Limitations:	• The sample size calculation is not described. • Lowest level of quantification for HPLC and triple quadrupole MS spectrometry is not stated. This means there is no indication of the level of sensitivity of the pharmacokinetic data. • The study did not control for gender differences in drug pharmacokinetics. • There was no concurrent placebo group in the study. For this reason, it could not be definitively stated whether the significant increase in plasma BUN and ALP were due to environmental or experimental factors. • Blood biochemical analysis was only completed after 5 days of administration. This may have excluded acute biochemical analyte changes due to damage which may have occurred in the first 4 days of meloxicam administration, resulting in an underestimation of any damage caused by the dose rate. • The study did not assess the maximum concentration achieved on days 1 to 4 of the multi-dose administration as the blood samples were taken too early. As the study compared the area under the curve (AUC) for plasma concentrations between the single and multiple dose trials, the calculated level of plasma accumulation may have been underestimated. • There was no statement of the frequency or system used for assessing behaviour and stress, or whether there were multiple observers. This may mean the assessments of the subjects were inconsistent. • There was minimal genetic diversity in the sample of subjects, and only healthy, young rabbits selected. This sample is not representative of the animals that would require analgesia in a clinical setting, such as surgical patients or sick rabbits. Thus, the pharmacokinetics and safety demonstrated by this study may not be generalisable to the target population. Additionally, the breed of rabbit chosen is uncommonly used as pets, further reducing the generalisability of the study results.

Delk et al. (2014)[5] *Prospective clinical trials addressing liver and kidney biochemical analytes*	
Population:	Three-month-old (sexually immature), healthy New Zealand white rabbits (*Oryctolagus cuniculus*) of unstated gender, all from the same commercial source, bred to be free from *Pasteurella* spp. and weighing 2.55–2.71 kg.
Sample size:	Six rabbits
Intervention details:	• The sample size was not split into groups. • The subjects were habituated to the environment and handling for 5 days before commencement of the study. • All subjects were administered 1 mg/kg of meloxicam solution orally via a 3 ml syringe every 24 hours for 29 days. • On days 1, 8, 15, 22, and 29, blood samples were collected immediately before (0 hours) meloxicam administration, then 2, 4, 6, 8 and 24 hours after administration. Blood collection was also completed 36 hours after the final meloxicam dose on day 29. • Rabbits were then euthanised with 100 mg/kg IV pentobarbital solution. A necropsy was conducted on each subject within 15 minutes of death.
Study design:	Prospective clinical trial

Outcome studied:	• Plasma concentrations of meloxicam were measured in all blood samples after the first dose, using HPLC and triple quadrupole MS. Samples at each concentration were validated (accuracy and coefficient of variation values stated within paper). Pharmacokinetic analysis was completed with software. • Packed cell volume and plasma biochemistry, measuring glucose, BUN, creatinine, total protein, albumin, globulin, total calcium, phosphorus, sodium, potassium, chloride, bicarbonate, cholesterol, and total bilirubin concentrations. CK, ALT, and ALP activities were measured. This was completed in each blood sample at 0 hours and the final sample on day 29. • Gross findings on necropsy and histopathological examination by a Board Certified histopathologist for lesions suggestive of acute or chronic meloxicam toxicosis. The organs examined histologically were lung, trachea, liver, spleen, kidneys, urinary bladder, salivary glands, mesenteric lymph nodes, oesophagus, fundus and pylorus of the stomach, small intestine, caecum, appendix, large colon, small colon, heart, skeletal muscles, adrenal glands, pancreas, and bone marrow. • Behaviour, food and water consumption, and urinary and faecal output were monitored subjectively by the same person daily. The weight of each subject was measured weekly.
Main findings: (relevant to PICO question):	• The blood and serum values remained within reference limits for all subjects for the duration of the study, and there were no significant changes. • No lesions were found grossly or histologically that suggested adverse effects due to meloxicam. • Mean peak plasma concentration of meloxicam at 1 mg/kg at day 1, 8, 15, 22, and 29 were 0.67 +/- 0.19 ug/ml, 0.81 +/- 0.21 ug/ml, 1.00 +/- 0.31 ug/ml, 1.00 +/- 0.29 ug/ml, and 1.07 +/- 0.19 ug/ml, respectively. • Plasma concentrations of meloxicam considered therapeutic in dogs (0.82 ug/ml[17]) and humans (0.92 ug/ml for a single dose, 1.94 ug/ml after 5 days of dosing[18]) were achieved in rabbits through a dose rate of 1 mg/kg. • There was plasma accumulation, at concentrations that were expected by the authors. • Average elimination half-life of meloxicam was approximately 7 hours after 29 days of dosing. • Statistical significance was accepted when $P < 0.05$. There were no significant pharmacokinetic differences for doses administered on day 8, 15, 22 or 29. However, there were significant differences in T max (h) day 1 vs. day 15; and day 1 vs. day 29; with no significant P value provided.
Limitations:	• The sample size calculation is not described. • Lowest level of quantification for the HPLC and triple quadrupole MS is not stated. This means there is no indication of the level of sensitivity of the pharmacokinetic data. • The study did not control for gender differences in drug pharmacokinetics. • There was plasma accumulation of the drug, which the researchers concluded was within expected limits. However, it was not reported how the researchers defined the expected limits for plasma accumulation. • The system used for assessing behaviour and stress was not stated. This may mean the assessments of the subjects were inconsistent. • Likewise 'behavior, attitude, mentation, activity, urinary and fecal output, and amount of food and water consumed by the rabbits were subjectively monitored'. The authors do not explain what 'subjective' monitoring entails. • There was minimal genetic diversity in the sample of subjects, and only healthy, young rabbits selected. This sample is not representative of the animals that would

	require analgesia in a clinical setting, such as surgical patients or sick rabbits. Thus, the pharmacokinetics and safety demonstrated by this study may not be generalisable to the target population. Additionally, the breed of rabbit chosen is uncommonly used as pets, further reducing the generalisability of the study results.

Cooper et al. (2009)[4] *Randomised controlled trial addressing liver and kidney biochemical analytes*	
Population:	Female Dutch Belted rabbits (a different breed of *Oryctolagus cuniculus* than New Zealand White) of unstated ages, all from the same commercial source, bred to be free from many common pathogens; weighing 2–3 kg.
Sample size:	29 rabbits
Intervention details:	• The subjects were habituated to the environment and diet for 5 to 7 days before commencement of the study. • The surgical intervention was an ovariohysterectomy, with the subjects induced by intramuscular ketamine 25 mg/kg with diazepam 0.3 mg/kg and maintained via face mask by isoflurane (2–4%) and oxygen (2 L/min). Length of incision, suture type, and closure method were the same for all subjects. The subjects were monitored for respiratory and heart rates, oxygenation (via pulse oximetry), cardiac rhythm (via electrocardiography), end-tidal CO_2 (capnography) and blood pressure (non-invasive). • After surgery, all subjects were recovered in a warmed environment before returning to their cages. • Subjects were randomised into three groups, and their respective postoperative treatments were administered as outlined below: – Buprenorphine group (10 subjects), at 0.03 mg/kg intramuscularly every 12 hours for 48 hours. – Meloxicam group (10 subjects), at 0.2 mg/kg every 24 hours for 48 hours. – Bupivacaine 0.5% group (nine subjects), with a single dose of 0.5 ml infused at the incision site postoperatively. • Animals were monitored for 7 days postoperatively.
Study design:	Randomised controlled trial
Outcome studied:	• The following parameters were assessed daily by the same unblinded observer from day 0 (before surgery) to day 7 postsurgery: – Food intake and faecal production were objectively measured. – Urine output was subjectively recorded (volume unquantified). – Abdominal palpation and auscultation, respiratory and heart rates, mucous membrane colour, and character of the surgical incision. • The following parameters were also assessed on day 0, day 2, and day 5: – Blood analysis, including complete blood count, haematocrit, glucose, BUN,

	creatinine, sodium, and potassium. – Body weights and rectal temperatures were objectively measured. – Rectal aerobic and anaerobic cultures were completed on rectal swabs.
Main findings: (relevant to PICO question):	• Postoperatively up to day 7, subjects in both the meloxicam and buprenorphine groups produced urine, remained hydrated, and had a normal body temperature, rectal culture, abdominal auscultation and palpation, and bloodwork. There were no significant differences for these parameters between the meloxicam and buprenorphine groups. This indicates meloxicam at 0.2 mg/kg was safe for administration over 2 days postoperatively in rabbits. • Several subjects in the bupivacaine group exhibited signs of gut stasis by day 2, and were given metoclopramide, subcutaneous fluids, and Timothy hay. This led to a more rapid return to normal food consumption and faecal production than both the meloxicam and buprenorphine groups, resulting in the researchers concluding the other groups would have benefitted from this adjunctive treatment. • Treatment with meloxicam 0.2 mg/kg resulted in a faster return to normal food consumption than treatment with buprenorphine, returning to normal consumption by day 5. • All groups had a 90% decrease in faecal production on day 1, with meloxicam treated rabbits producing the largest amount (significant only compared to the bupivacaine group P = 0.0256).
Limitations:	• The sample size calculation is not described. • The study did not control for age-related differences in drug pharmacokinetics and safety. • There was minimal genetic diversity in the sample of subjects selected. Thus, although the potential for confounding was reduced by this, the safety demonstrated by this study may be less generalisable to the target population. Additionally, the breed of rabbit chosen is uncommonly used as pets, further reducing the generalisability of the study results. • The duration of anaesthesia was unspecified, so the amount of patient compromise caused by the anaesthetic may have been inconsistent, potentially confounding the data.

Goldschlager et al. (2013)[7] *Randomised controlled trial addressing liver and kidney biochemical analytes, and pain behaviour*	
Population:	Male New Zealand white rabbits (*Oryctolagus cuniculus*), two to three-months-old (sexually immature), all from the same commercial source, bred to be free from many common pathogens, and weighing approximately 3 kg.
Sample size:	39 rabbits

Intervention details:	• The subjects were allowed to habituate to the environment and diet for 7 days, then were placed on a high cholesterol diet (to meet the needs of a different experiment) before commencement of the present study. • The surgical intervention (day 0) was a vascular cut-down of the femoral artery, with the subjects induced by intramuscular ketamine 30 mg/kg with xylazine 2 mg/kg, and received oxygen (2 L/min) via face mask. Suture type and closure method were the same for all subjects. The respiration rate, heart rate, and oxygenation (via pulse oximeter) of the subjects were monitored. • After surgery, all subjects recovered in their cages. • Subjects were randomised into four groups, and their respective treatments were administered as outlined below: – Meloxicam group (10 subjects), at 0.2 mg/kg subcutaneously every 24 hours for 3 days. – Buprenorphine group (10 subjects), at 0.03 mg/kg subcutaneously every 12 hours for 3 days. – Combined meloxicam-buprenorphine group (10 subjects), at 0.1 mg/kg and 0.01 mg/kg, respectively, subcutaneously every 24 hours for 3 days. – Bupivacaine 0.5% group (nine subjects), with a single dose of 0.5 ml infused at the incision site at the time of surgery. • Animals were monitored for 28 days postoperatively by three veterinary technicians.
Study design:	Randomised controlled trial
Outcome studied:	• Body weights on days 0 (prior to surgery), day 7, day 14, day 21, and day 28. • Complete blood count, haematocrit, BUN, creatinine, glucose, ALT, ALP, total protein, potassium, calcium, sodium, phosphorus, and rectal swabs for gram staining were conducted prior to the surgery on day 0, and again on day 7. Blood samples were collected from subjects while they were anaesthetised. • Faecal corticosterone metabolites (FCM) were measured with a 5α-pregnane-3β,11β,21-triol-20-one enzyme immunoassay, on faecal samples collected in the mornings on day 0 (prior to surgery), day 3, day 7, day 14, day 21, and day 28. • Food intake, faecal production, urine output, and behaviour were monitored subjectively.
Main findings: (relevant to PICO question):	• FCM rose from day 1 to day 7 during treatment in the meloxicam, bupivacaine, and buprenorphine groups. Whereas in the combined meloxicam-buprenorphine group FCM did not begin rising until day 3 when the analgesic treatment was discontinued. This indicates meloxicam at 0.2 mg/kg provided inadequate analgesia postoperatively when used alone. It also indicates that a low dose of meloxicam may provide effective pain relief when in combination with buprenorphine. • The four groups all reached similar peak levels of FCM. The researchers hypothesised that this was due to the combined meloxicam-buprenorphine anaesthetic protocol being discontinued too early, and the other groups providing inadequate analgesia, causing the rabbits to experience postoperative pain and stress. • All treatment groups lost weight, but the low dose meloxicam-buprenorphine group displayed least amount of weight loss over 7 days than the other treatment groups. • All subjects remained within the reference ranges for complete blood counts and serum biochemistry, and had normal faecal flora, indicating the treatment protocols tested are safe for rabbits at these dose rates for 7 days. This also indicates that FCM is a more sensitive indicator of stress and efficacy of analgesia than these variables.

	• There was no significant difference (significance defined as $P \leq 0.05$) in the quantity of food consumed and faecal output between groups. • Active behaviour was reduced in all groups postoperatively, potentially indicative of postoperative pain or sedation due to analgesia. Inactivity began to decline in all groups during day 1 to day 7.
Limitations:	• The sample size calculation is not described. • There was minimal genetic diversity in the sample of subjects, and only young rabbits were selected. Additionally, the breed of rabbit chosen is uncommonly used as pets, reducing the generalisability of the study results. • The surgical monitoring did not include blood pressure or capnography, and thus may have missed any rabbits that became hypothermic or suffered from hypoventilation during the procedure. Additionally, it was not stated whether any supplemental heat was provided during recovery, which may have exacerbated any hypothermia in the subjects and prolonged the recovery and healing. This could have potentially increased the level of glucocorticoid release, thus FCM levels, and altered the pharmacokinetic profile of the drugs within any affected animals, impacting the level of analgesia received and confounding the data. • The duration of anaesthesia was unspecified, so the amount of patient compromise caused by the anaesthetic may have been inconsistent, potentially confounding the data. • Three unblinded observers were used to collect data, including subjective assessment of faecal and urine output, behaviour, and food consumed, potentially introducing bias due to multiple observers. The authors do not explain the method/s of subjective assessment. • The rabbits were anaesthetised to collect blood on day 7, which could have created stress for the subjects due to handling and post-anaesthesia recovery, resulting in iatrogenic increased FCM levels. This could have created confounding bias. • The treatments were only administered for 3 days, which appears to be inadequate based on the rise in FCM levels in the combined meloxicam-buprenorphine group after discontinuation. Acute postoperative pain has been defined as lasting up to 7 days after the procedure. Thus, it would have been beneficial to extend the duration of the treatment protocols to match the more likely duration of the pain. This may have given a more realistic indication of their efficacies over time.

Leach et al. (2009)[8] *Randomised controlled trial addressing pain behaviour*	
Population:	Three-month-old (sexually immature), clinically normal, female New Zealand white rabbits (*Oryctolagus cuniculus*) all from the same commercial source, bred to be free from many common pathogens, and weighing 1.8–2.3 kg.
Sample size:	28 rabbits

Intervention details:	• The subjects habituated to the environment, handling, and video monitoring equipment for 14 days before commencement of the study. • Subjects were randomised into four groups of seven, and their respective treatments (outlined below) were administered orally one hour before surgery (occurring between 9–10:30am) on day one, then at 9am on the following 2 days. • Treatments: – Placebo group received 2 ml/kg saline solution on day 1 to day 3. – Low dose group received 0.2 mg/kg meloxicam on day 1 (before surgery), and 0.1 mg/kg meloxicam on day 2 and day 3. – Medium dose group received 0.6 mg/kg meloxicam on day 1, and 0.3 mg/kg meloxicam on day 2 and day 3. – High dose group received 1 mg/kg meloxicam on day 1 (before surgery), and 0.5 mg/kg meloxicam on day 2 and day 3. • The surgical intervention was an ovariohysterectomy, with the subjects induced by intravenous propofol 10 mg/kg, and maintained under intubation by sevoflurane (4–6%) and oxygen (3–3.5 L/min). Duration of anaesthesia, length of incision, suture type, and closure method were the same for all subjects. • After surgery, all subjects recovered in an incubator before they were returned to their cages for the duration of the study.
Study design:	Randomised controlled trial
Outcome studied:	• Body weight, food and water consumption were collected daily by a single, treatment blinded observer before application of the treatments. • Behavioural data was recorded at specific time points throughout the study, via a remotely operated digital video camera placed in front of the cages. This data was recorded by one treatment blinded observer and analysed by software to calculate frequency and duration of behaviours.
Main findings: (relevant to PICO question):	• There were significant differences ($P \leq 0.05$) in behaviour between groups (listed below) that indicated the medium and high doses of meloxicam provide significantly more effective analgesia than the low dose of meloxicam. – Searching behaviour was displayed by subjects in the high-dose meloxicam group significantly more frequently than in the placebo group ($P \leq 0.05$). – Duration of food consumption over a 24h period immediately after surgery was significantly higher in the high and mid-dose meloxicam groups than the low dose group ($P < 0.0001$). – Duration of interaction with the environment and standing were both significantly higher in the mid-dose meloxicam group compared to the placebo group ($P < 0.001$). • Inactive pain behaviour was displayed in all groups after surgery, indicating none of the treatments provided complete analgesia. • There was no significant difference in body weight change or quantity of food or water consumed between the groups.
Limitations:	• The sample size calculation is not described. • There was minimal genetic diversity in the sample of subjects, and only healthy, young rabbits selected. Additionally, the breed of rabbit chosen is uncommonly used as pets, reducing the generalisability of the study results. • It was not specified what monitoring was conducted during the surgical procedures, thus it may not have been identified if some subjects experienced more traumatic surgeries. This could result in greater pain levels in some subjects, confounding the behavioural data for analgesic response.

	• It was not noted whether the methods used for measuring food and water consumption were subjective or objective.

Appraisal, application and reflection

Every study omitted discussion of calculations to determine the number of subjects required to provide adequate study power. It is possible that all studies had insufficient subjects per treatment group. Consequently some of the non-significant results may be an artefact of low power, limiting the reliability of each study's conclusions [16]. Additionally, the prospective clinical trials provided incomplete information on the safety of meloxicam dosages[5,6]. This is due to recruitment of subjects which did not represent the target population of rabbits that would be receiving meloxicam, such as postoperative and sick rabbits[5, 6]. However, the studies did demonstrate repeatable results, as no rabbit receiving either 0.2 mg/kg or 1 mg/kg orally, developed significant changes in haematology of serum biochemistry, including liver and kidney biochemical analytes[5, 6]. A safety profile, based on the absence of abnormal blood indices, was demonstrated for up to 29 days in one study[5].

This same study found no significant histological lesions indicative of meloxicam induced gastrointestinal toxicosis[5], which is important due to the potential for non-steroidal anti-inflammatories (NSAIDs) to induce gastrointestinal ulceration[19]. Furthermore, an excluded study demonstrated no significant changes in the faecal microbiota of rabbits when meloxicam was administered at a dose of 1 mg/kg, orally for 29 days indicating long-term treatment of meloxicam at this dosage does not cause gut dysbiosis in healthy rabbits[20].

Additional studies should be conducted with histopathological examination of the gastrointestinal tract, to confirm the safety of meloxicam in rabbits at a dosage ³ 1 mg/kg. There are also no studies comparing the activity of meloxicam to inhibit the cyclooxygenase (COX), COX1 and COX2 pathways in rabbits. It would be beneficial for further research to be conducted in this area to gain a greater understanding of the therapeutic plasma concentration in rabbits and the risk of adverse effects, especially as the COX2 selectivity of meloxicam may decrease with higher NSAID concentrations[21, 22].

Several studies are available that further add credence to the safety of meloxicam at dosages ³ 1 mg/kg in healthy, young rabbits. One study, which was excluded from the review as it did not investigate the nominated doses, demonstrated the safety of meloxicam at a dosage of up to 1.5 mg/kg for 5 days in rabbits, with no significant changes in biochemical analytes[9]. In addition, another excluded study noted no toxic effects after a single dose of 20 mg/kg of meloxicam in rabbits, although the methods used to reach this conclusion on toxicity were not explained[23]. Due to the lack of current evidence, rabbits with compromised liver and kidney function should still have serum biochemical analytes monitored when medicated with meloxicam, as it undergoes metabolism in the liver and is excreted via the urine and faeces[24]. Thus, unexpected accumulation and adverse effects may occur if these organs are compromised.

Studies on postoperative rabbits in two of the randomised controlled trials demonstrated no significant differences in blood variables after several days of meloxicam administration at 0.2 mg/kg[4, 7]. However, a third study which administered 1 mg/kg meloxicam to postoperative subjects did not provide blood data[8], so there is insufficient information to compare safety of the two doses postoperatively.

Four of the studies used the same breed of rabbit i.e. the New Zealand White Rabbit (*Oryctolagus cuniculus*)[5-8]. There is only one article on the effect of rabbit breed on drug metabolism[25], which indicated a significant difference in metabolism between pigmented and nonpigmented rabbits for a single, topical, ocular drug. This indicates there could be a significant difference between the drug metabolism in the chosen subjects of the current studies and the general population of rabbit patients, meaning the narrow sample population choice could impact the applicability of the studies in clinical practice. The topic covered by this review is not specific to breed or gender, so the available evidence may not provide a complete clinical picture to answer the PICO sufficiently. Likewise there are known to be gender and age differences to metabolise some drugs in many species [26, 27]. It is therefore unknown whether the lack of gender control in some of the current studies would have introduced bias to their results[5, 6].

The prospective clinical trial studies generated hypotheses for the efficacy of meloxicam as an analgesic in

rabbits at different dosages based on plasma concentrations[5, 6]. Conclusions about dosage in the current prospective clinical trials are drawn from comparisons of plasma concentration in dogs and humans[17, 18]. The therapeutic plasma concentration for rabbits is unknown as the use of meloxicam in this species is off label, with no clinical trials conducted on rabbits by drug companies. Also, although meloxicam has demonstrated a high plasma to tissue concentration ratio[2], it has preferential and marked distribution into chronically inflamed tissues in rats[28]. Thus, plasma concentration may not be a reliable indicator of efficacy of meloxicam for those rabbits requiring analgesia or having inflamed tissues.

Therefore, the best available evidence for the efficacy of different meloxicam dosages in rabbits is through pain behaviour studies. Although it is recognised that rabbits, unlike rodents, seem more likely to respond to pain and/or distress by remaining motionless (freezing for long periods)[9, 29]. This is termed inactive pain behaviour[8].

In one study it was found that the meloxicam treated group had a faster return to baseline food consumption compared to those treated with buprenorphine or bupivacaine[4]. The authors suggested that this indicated a greater level of analgesia[4]. However this is in contrast to two other similar studies where significant differences in other pain indicators were noted between treatment groups (as documented in the 'Summary of the evidence') but there was no noted difference in food consumption[7, 8]. Thus, it is unclear whether food consumption is a reliable indicator of pain in rabbits. NSAIDs like meloxicam are also known to have direct and indirect effects on the gastrointestinal tract mucosa[19], but in patients with no gastrointestinal risk factors, the incidence of gastrointestinal disturbance induced by oral meloxicam administration is considered low [30]. So, it would be unlikely that meloxicam administration alone would result in significant differences in food intake due to nausea in these rabbit studies.

Only two studies exist which analyse pain behaviour in rabbits receiving meloxicam at 0.2 mg/kg and 1 mg/kg[7, 8]. The lower dose rate of 0.2 mg/kg was deemed inadequate when used as the sole analgesia in both studies, with both behaviour and FCM indicating the presence of significant postoperative pain[7, 8]. This was demonstrated for both major and minor surgical pain, with an ovariohysterectomy and endarterectomy, respectively[7, 8]. Higher dose rates of meloxicam administered after the ovariohysterectomies, were associated with greater levels of activity, indicating decreased levels of postoperative pain[8]. This study provides limited evidence, as the 1 mg/kg was only assessed for the first day postoperatively before decreasing the dosage to 0.5 mg/kg/day for 2 days[8].

Nonetheless, the presence of inactive pain behaviour at every dose rate tested indicated a daily dosage greater than 1 mg/kg may be required to achieve complete analgesia in rabbits the first day after abdominal surgery, and greater than 0.5 mg/kg for the next 2 days[8]. In comparison, a suggested therapeutic dose rate of oral meloxicam in dogs is 0.2 mg/kg, followed by a maintenance rate of 0.1 mg/kg[31]. This difference in dose rate efficacy is likely due to a comparatively higher metabolic rate in rabbits than dogs, resulting in faster drug clearance. This is evidenced by the short terminal half-life of approximately 8 hours, consistently found for meloxicam in rabbits[3, 5, 6, 9], compared to an elimination half-life of approximately 12 to 38 hours in dogs[2, 32]. Further research on pain behaviour at a dose rate of 1 mg/kg or greater, and potentially considering more frequent dosing, for example, bi-daily, would be beneficial.

Recently reported surgical case studies in rabbits include stabilisation of a calcaneus fracture whereby a meloxicam dosage of 1 mg/kg was administered by subcutaneous injection (s.c.) every 12 h both pre and postoperatively combined with buprenorphine (50 µg/kg s.c. every 6 h). Another describes a partial glossectomy whereby meloxicam was administered at 1 mg/kg s.c. once daily for 5 days postoperatively [34]. One study describes removal of a transitional cell carcinoma from the bladder apex with a postoperative meloxicam dosage of 0.5 mg/kg orally, every 12 hours for 5 days[35]. Thus, there may be emerging evidence for more frequent dosing and higher dose rates.

As an alternative, it was shown that a multimodal analgesic protocol of low dose-rate meloxicam and buprenorphine prevented an increase in faecal corticosterone metabolites (FCM) postoperatively until treatment was discontinued after 2 days[7]. FCM measurement is an accepted non-invasive method of assessing stress in animals[36] with the caveat that FCM can also increase with arousal for any reason. However, active behaviour was decreased postoperatively from days 1 to day 7 with no difference noted between treatment groups, potentially indicating full analgesia was not achieved[7]. The lack of an objective pain behaviour

measurement system in this study limits the usefulness of this data, as subjective measurements may not have the sensitivity required to distinguish significant changes in behaviour. Further studies investigating meloxicam in multimodal treatment protocols at different dose rates and for a longer duration would be useful.
In conclusion, the limited number of studies available indicates that 0.2 mg/kg meloxicam when used alone is an ineffective analgesic in rabbits postoperatively[7,8]. There is some evidence for a lower dose rate providing effective analgesia when multimodal treatment is provided with low dose buprenorphine[7]. The higher dose-rate of 1 mg/kg may also be inadequate analgesia postoperatively, based on a single study, but it was demonstrated that as the dose rate of meloxicam was increased, the rabbits demonstrated normal behaviours at a greater frequency[8]. There is reasonable evidence that meloxicam is safe for rabbits at both 0.2 mg/kg and 1 mg/kg[4-7,9], although any animal with a compromised kidney or liver function should be monitored. Thus, based on the current evidence, it would be beneficial to choose the higher recommended daily dose rate of 1 mg/kg when using meloxicam for analgesia in rabbits and consider multimodal analgesia for severe pain postoperatively.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts via Web of Science Platform (1973-present) Medline via OVID SP (1946-present)
Search terms:	(rabbit OR "oryctolagus cuniculus") AND (meloxicam OR metacam) AND (blood OR behaviour OR pain OR "pain, postoperative")
Dates searches performed:	11th August 2018

Exclusion / Inclusion Criteria	
Exclusion:	Articles not relevant to the PICO question, article summaries, literature reviews, case reports, case studies, conference proceedings.
Inclusion:	Articles relevant to the PICO question, randomised controlled trials, prospective clinical trials.

Search Outcome

Database	Number of results	Excluded – literature review	Excluded – Article summary	Excluded – Conference proceedings	Excluded – Case report/study	Excluded – irrelevant to PICO	Total relevant papers
CAB Abstracts	25	5	1	2	3	9	5
Medline	3	0	0	0	0	1	2
Total relevant papers when duplicates removed							**5**

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Mayer J, Brown S, Mitchell MA. Survey to investigate owners' perceptions and experiences of pet rabbit husbandry and health. *J Exot Pet Med* 2017;26:123–131. DOI: http://dx.doi.org/10.1053/j.jepm.2017.01.021
2. Busch U, Schmid J, Heinzel G et al. Pharmacokinetics of meloxicam in animals and the relevance to humans. *Drug Metab Dispos* 1998;26:576–584. http://dmd.aspetjournals.org/content/26/6/576.long
3. Carpenter JW, Pollock CG, Koch DE et al. Single and multiple-dose pharmacokinetics of meloxicam after oral administration to the rabbit (*Oryctolagus cuniculus*). *J Zoo Wildl Med* 2009;40:601–606. DOI: http://dx.doi.org/10.1638/2007-0115.1
4. Cooper CS, Metcalf-Pate KA, Barat CE et al. Comparison of side effects between buprenorphine and meloxicam used postoperatively in Dutch Belted Rabbits (*Oryctolagus cuniculus*). *J Am Assoc Lab Anim Sci* 2009;48:279–285. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2696831/
5. Delk KW, Carpenter JW, KuKanich B et al. Pharmacokinetics of meloxicam administered orally to rabbits (*Oryctolagus cuniculus*) for 29 days. *Am J Vet Res* 2014;75:195–199. DOI: http://dx.doi.org/10.2460/ajvr.75.2.195
6. Fredholm DV, Carpenter JW, KuKanich B et al. Pharmacokinetics of meloxicam in rabbits after oral administration of single and multiple doses. *Am J Vet Res* 2013;74:636–641. DOI: http://dx.doi.org/10.2460/ajvr.74.4.636
7. Goldschlager GB, Gillespie VL, Palme R et al. Effects of multimodal analgesia with low-dose buprenorphine and meloxicam on fecal glucocorticoid metabolites after surgery in New Zealand white rabbits (*Oryctolagus cuniculus*). *J Am Assoc Lab Anim Sci* 2013;52:571–576. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3784663/
8. Leach MC, Allweiler S, Richardson C et al. Behavioural effects of ovariohysterectomy and oral administration of meloxicam in laboratory housed rabbits. *Res Vet Sci* 2009;87:336–347. DOI: https://doi.org/10.1016/j.rvsc.2009.02.001
9. Turner PV, Chen CH, Taylor MW. Pharmacokinetics of meloxicam in rabbits after single and repeat oral dosing. *Comp Med* 2006;56:63–67. https://www.ingentaconnect.com/content/aalas/cm/2006/00000056/00000001/art00009%3bjsessionid=4b77h4ann1r0e.x-ic-live-01
10. Holzer P. Treatment of opioid-induced gut dysfunction. *Expert Opin Investig Drugs* 2007;16:181–194. DOI: http://dx.doi.org/10.1517/13543784.16.2.181
11. Luna SPL, Basílio AC, Steagall PVM et al. Evaluation of adverse effects of long-term oral administration

of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. *Am J Vet Res* 2007;68:258–264. DOI: http://dx.doi.org/10.2460/ajvr.68.3.258

12. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. *Neurogastroenterol Motil* 2004;16:17–28. DOI: http://dx.doi.org/10.1111/j.1743-3150.2004.00554.x
13. Harcourt-Brown F. Critical and emergency care of rabbits. *Veterinary Nursing Journal* 2011;26:443–456. DOI: http://dx.doi.org/10.1111/j.2045-0648.2011.00119.x
14. Fisher P, Graham J. Rabbits. In: Carpenter JW, editor. *Exotic Animal Formulary*. 5 edn. Elsevier, St Louis, 2017:708–760.
15. Costantino G, Montano N, Casazza G. When should we change our clinical practice based on the results of a clinical study? The hierarchy of evidence. *Intern Emerg Med* 2015;10:745–747. DOI: http://dx.doi.org/10.1007/s11739-015-1230-8
16. Brown SJ. *Evidence-based nursing: the research-practice connection*. Jones and Bartlett Publishers, Sudbury, Mass, 2008.
17. Montoya L, Ambros L, Kreil V et al. A pharmacokinetic comparison of meloxicam and ketoprofen following oral administration to healthy dogs. *Vet Res Commun* 2004;28:415–428. DOI: http://dx.doi.org/10.1023/B:VERC.0000034995.81994.49
18. Hanft G, Türck D, Scheuerer S et al. Meloxicam oral suspension: a treatment alternative to solid meloxicam formulations. *Inflamm Res* 2001;50:35–37. DOI: http://dx.doi.org/10.1007/PL00000219
19. Wallace JL. How do NSAIDs cause ulcer disease? *Best Pract Res CL GE* 2000;14:147–159. DOI: http://dx.doi.org/10.1053/bega.1999.0065
20. Eshar D, Weese JS. Molecular analysis of the microbiota in hard feces from healthy rabbits (*Oryctolagus cuniculus*) medicated with long term oral meloxicam. *BMC Vet Res* 2014;10:62-62. DOI: https://doi.org/10.1186/1746-6148-10-62
21. Kay-Mugford P, Benn SJ, LaMarre J et al. In vitro effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. *Am J Vet Res* 2000;61:802–810. DOI: http://dx.doi.org/10.2460/ajvr.2000.61.802
22. Pairet M, van Ryn J, Schierok H et al. Differential inhibition of cyclooxygenases-1 and -2 by meloxicam and its 4'-isomer. *Inflamm Res* 1998;47:270–276. DOI: http://dx.doi.org/10.1007/s000110050329
23. Salhab AS, Gharaibeh MN, Shomaf MS et al. Meloxicam inhibits rabbit ovulation. *Contraception* 2001;63:329–333. DOI: http://dx.doi.org/10.1016/S0010-7824(01)00207-4
24. Davies N, Skjodt N. Clinical pharmacokinetics of meloxicam: a cyclo-oxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clin Pharmacokinet* 1999;36:115–126. DOI: http://dx.doi.org/10.2165/00003088-199936020-00003
25. Lee VH, Hui HW, Robinson JR. Corneal metabolism of pilocarpine in pigmented rabbits. *Invest Ophthalmol Vis Sci* 1980;19:210–213. https://iovs.arvojournals.org/article.aspx?articleid=2159095
26. Depelchin B, Bloden S, Michaux C et al. Effects of age, sex and breed on antipyrine disposition in calves. *Res Vet Sci* 1988;44:135–139. DOI: https://doi.org/10.1016/S0034-5288(18)30828-2

27. Hay Kraus B, Greenblatt D, Venkatakrishnan K et al. Evidence for propofol hydroxylation by cytochrome P4502B11 in canine liver microsomes: breed and gender differences. *Xenobiotica* 2000;30:575–588. DOI: https://doi.org/10.1080/004982500406417
28. Busch U, Engelhardt G. Distribution of [14C]meloxicam in joints of rats with adjuvant arthritis. *Drugs Exp Clin Res* 1990;16:49-52. https://www.ncbi.nlm.nih.gov/pubmed/1698136
29. Johnston M. Clinical approaches to analgesia in ferrets and rabbits. *Semin Avian Exot Pet Med* 2005;14:229–235. DOI: https://doi.org/10.1053/j.saep.2005.09.003
30. Martin RM, Biswas P, Mann RD. The incidence of adverse events and risk factors for upper gastrointestinal disorders associated with meloxicam use amongst 19087 patients in general practice in England: cohort study. *Brit J Clin Pharmaco* 2000;50:35–42. DOI: https://doi.org/10.1046/j.1365-2125.2000.00229.x
31. Plumb DC. *Plumb's veterinary drug handbook*. 6th edn. PharmaVet, Ames, Iowa, 2008.
32. Yue Y, Xiao-yan C, San-ming L et al. Pharmacokinetic studies of meloxicam following oral and transdermal administration in Beagle dogs. *Acta Pharmacol Sin* 2009;30:1060–1064. DOI: http://dx.doi.org/10.1038/aps.2009.73
33. Volait-Rosset L, Pignon C, Manou M et al. Surgical management of a calcaneus fracture in a pet rabbit. *J Exot Pet Med* 2019;29:110–114. DOI: https://doi.org/10.1053/j.jepm.2018.11.003
34. Bulliot C, Flenghi L, Levrier C. Lingual sarcoma and its treatment with partial glossectomy in a pet rabbit (*Oryctolagus cuniculus*). *J Exot Pet Med* 2019;29:70–75. DOI: https://doi.org/10.1053/j.jepm.2018.08.006
35. Cikanek SJ, Eshar D, Nau M et al. Diagnosis and surgical treatment of a transitional cell carcinoma in the bladder apex of a pet rabbit (*Oryctolagus cuniculus*). *J Exot Pet Med* 2018;27:113–117. DOI: https://doi.org/10.1053/j.jepm.2018.02.004
36. Palme R, Rettenbacher S, Touma C et al. Stress hormones in mammals and birds: comparative aspects regarding metabolism, excretion, and noninvasive measurement in fecal samples. *Ann N Y Acad Sci* 2005;1040:162–171. DOI: http://dx.doi.org/10.1196/annals.1327.021