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Should doses exceeding 0.2 mg/kg of oral meloxicam be given to reduce surgical recovery time in rabbits and should twice daily administration be considered?

A Knowledge Summary by

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ISSN: **2396-9776**
Published: **22 Jul 2021**
in: **The *Veterinary Evidence* journal Vol 6, Issue 2**
DOI: **https://doi.org/10.18849/ve.v6i3.372**
Reviewed by: **Laura Dixon (BSc(Hons) PhD) and Rebecca Schofield (RVN BSc Hons)**
Next Review Date: **29 Mar 2023**

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KNOWLEDGE SUMMARY

PICO question

In reducing surgical recovery time in rabbits (*Oryctolagus cuniculus*), should doses exceeding 0.2 mg/kg of oral meloxicam be given and is twice daily administration more effective than a single daily dose?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

Nine papers were critically reviewed, yet no studies were found to directly investigate the effects of twice daily dosing with meloxicam postoperatively in rabbits. There were five descriptive, non-comparative case series; two nonblinded parallel group randomised control trials; one blinded, placebo-controlled parallel group randomised trial and one prospective, randomised crossover trial

Strength of evidence

Weak

Outcomes reported

The current recommended oral dose of meloxicam in rabbits of 0.2–0.3 mg/kg once a day was consistently described as inadequate for postoperative analgesia following surgery (Delk et al., 2014). Instead, higher doses of 1–1.5 mg/kg were required to reach a similar peak plasma concentration as found to be clinically effective in other species, such as canines, and provide a better degree of analgesia in rabbits (Montoya et al., 2004; and Delk et al., 2014). Although no studies were found evaluating twice daily administration of meloxicam, the available evidence suggests a dose exceeding 0.2–0.3 mg/kg daily is required for adequate postoperative analgesia in rabbits. Whether this increased dose could be given twice daily should be investigated, providing scope for future research

Conclusion

Further studies are required to directly assess the benefits of twice daily oral meloxicam. However, it is possible that a dose exceeding 0.2–0.3 mg/kg is required and therefore higher doses should be considered in these studies

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

You are a veterinarian working in a first opinion small animal practice and have scheduled a routine ovariohysterectomy on a rabbit. You perform the surgery, which went well, and the patient is now ready to be discharged. You know that you will need to send the rabbit home with some pain medication to aid their recovery after surgery, so plan to prescribe meloxicam, as the only clinically licensed drug for pain relief in rabbits. However, you are unsure whether the recommended dosage should be increased to provide adequate pain relief, and whether medication should be given once or twice daily to reduce postoperative pain as much as possible, as the current indication is considered low by some sources (Turner et al., 2006; Carpenter et al., 2009; and Delk et al., 2014).

The evidence

Nine papers were critically reviewed. These included five descriptive, non-comparative case series; two nonblinded parallel group randomised control trials; one blinded, placebo-controlled parallel group randomised trial and one prospective, randomised crossover trial. As none of the papers directly studied the effects of twice daily dosing with meloxicam and there was only one blinded randomised control trial, the strength of the evidence relating to the PICO question is weak. Further studies are required to provide stronger evidence answering the query.

Summary of the evidence

Eshar & Weese (2014)	
Population:	3 month old, entire female New Zealand white rabbits. All weighed between 2.52–2.71 kg and were free from specified *Pasteurella* spp.
Sample size:	Six rabbits

Intervention details:	• All rabbits were housed individually at a temperature of 21°C, with 16 hours of light and 8 hours of dark provided each day.
	  ○ Rabbits were fed ad libitum water and a free choice of timothy hay and pelleted diet.
	  ○ They were left to acclimate to the research facility for 5 days and were 'habituated' to handling before the study began.
	• Each rabbit was clinically assessed through a physical exam, complete blood count, serum biochemistry and urinalysis prior to the study. They were shown to demonstrate normal behaviour. This was assessed subjectively following a thorough physical exam.
	• Each rabbit was given 1 mg/kg meloxicam once daily, orally for 29 days.
	• The rabbits' behaviour including activity, eating, drinking and defecation, was assessed daily by the researchers.
	• 10 fresh faecal samples were collected from each rabbit. At 08:00 on days 0 (prior to treatment beginning), 6, 14 and 21.
	  ○ Therefore, a total of four faecal samples were collected from each rabbit throughout the study.
	• DNA was extracted from the faeces via Polymerase Chain Reaction (PCR) for detection of pathogens.
	• The microbiome of the hard faeces was assessed using the MOTHUR algorithm (Schloss et al., 2009) package.
	  ○ The relative abundancies of microorganisms were compared between rabbits.

Study design:	Descriptive, non-comparative case series
Outcome studied:	• The faecal bacterial microbiota was objectively assessed to determine the impact of long-term administration of meloxicam on the gut microbiome of rabbits. • The rabbits' behaviour was assessed subjectively by the researchers. It was not specified how this was determined or whether an ethogram was used.

Main findings: (relevant to PICO question):	• There were no apparent behavioural changes reported between rabbits.
	• There was minimal difference in the faecal microbiota population structures identified between timepoints.
	  ○ No significant difference detected with the Yue & Clayton measure of dissimilarity using an Analysis of Molecular Variance (AMOVA), (P = 0.082).
	  ○ Significant differences were found with the Jaccard index (a measure of community membership) using an AMOVA, (P = 0.011) between days 0–21 (P = 0.002) and days 14–21 (P = 0.030).
	• Study suggests that 1 mg/kg of oral meloxicam administered once daily is safe for use clinically in rabbits with minimal gastrointestinal side effects.

Limitations:	• The behaviour of the rabbits was subjectively assessed by the researchers and so the potential for bias or variation in behavioural interpretations remains strong.
	  ○ Behavioural changes in rabbits cannot be relied upon as the sole indicator of pain.
	  ○ Pain levels were not assessed in the rabbits using an accepted scale such as the Rabbit Grimace Scale (RbtGS).
	  ○ The study does not consider rabbits that were recovering from surgery.
	• This study was carried out on healthy laboratory rabbits rather than pet rabbits and it does not consider a veterinary context.
	• Only faecal samples were analysed and therefore this may not be a true reliable representation of the overall gut health of the rabbits.
	• A small sample size was used and there was no control group.
	• Only hard faeces were analysed and soft faeces were not considered.
	• Breed and sex differences were not considered.
	• The behaviour of the animals was not filmed – as rabbits are prey animals, the presence of the observer may have altered their behaviour.

Delk et al. (2014)	
Population:	3 month old, entire female New Zealand white rabbits. All weighed between 2.52–2.71 kg and were free from specified *Pasteurella* spp.
Sample size:	Six rabbits

Intervention details:	• All rabbits were housed individually at a temperature of 21°C, with 16 hours of light and 8 hours of dark provided each day.
	  ○ Rabbits were fed ad libitum water and a free choice of timothy hay and pelleted diet.
	  ○ They were left to acclimate to the research facility for 5 days and were 'habituated' to handling before the study began.
	• Each rabbit was clinically assessed through a physical exam, complete blood count, serum biochemistry and urinalysis prior to the study. They were determined to be behaviorally normal, although the criteria for determining this was not specified by the authors.
	• Each rabbit was given 1 mg/kg meloxicam orally every 24 hours for 29 days.
	• The rabbits' behaviour including activity, eating, drinking and defecation was assessed daily.
	• Blood samples were collected from either the lateral saphenous vein or auricular artery of each rabbit at 0 (prior to meloxicam administration), 2, 4, 6, 8 and 24 hours after meloxicam administration on days 1, 8, 15, 22 and 29 during the treatment.
	  ○ At each 0 timepoint and at an additional timepoint 36 hours after the final meloxicam dose on day 29, 1.5 ml of blood was collected for packed cell volume (PCV) and pharmacokinetic analysis.
	  ○ At all the other timepoints, 0.5 ml of blood was collected for pharmacokinetic analysis.
	  ○ A total of 31 blood samples were taken from each rabbit throughout the duration of the study.
	• Each rabbits' behaviour was monitored subjectively by a single investigator throughout the study and they were weighed weekly. The study does not specify how the behaviour was monitored or whether an ethogram was used.
	• After the study, the rabbits were humanely euthanised and a post-mortem necroscopy was carried out for any gross abnormalities.

Study design:	Descriptive, non-comparative case series

Outcome studied:	• Pharmacokinetic parameters.
	  ○ AUC0-24 – Area under the curve for plasma concentration vs time. From administration of dose to 24 hours afterwards.
	  ○ AUCinf – Area under the curve for plasma concentration vs time. Curve extrapolated to infinity following administration of a single dose.
	  ○ Cmax – Maximum plasma concentration of meloxicam.
	  ○ Time to maximum plasma concentration.
	  ○ Terminal half life.

	• Behaviour of the rabbits. • Weight of the rabbits each week. • Blood sample analysis including biochemistry. • Post-mortem gross abnormalities.

Main findings: (relevant to PICO question):	• There were no apparent adverse reactions to meloxicam administered at this dose throughout the study, suggesting it is well tolerated orally.
	  ○ There were no changes in behaviour, food or water consumption, activity or faecal production.
	  ○ There were no post-mortem findings which could be attributed to meloxicam toxicity.
	• There was no significant difference detected for any pharmacological parameter assessed between days 8, 15, 22 and 29.
	• The mean time to reach peak plasma concentration of meloxicam was 6.3 ± 0.8 hours, 5.3 ± 1.0 hours, 4.7 ± 1.0 hours, 5.0 ± 1.1 hours, and 4.3 ± 0.8 hours on days 8, 15, 22 and 29 respectively.
	• The peak plasma concentration of meloxicam achieved in this study was proportionally higher than the peak plasma concentration reached following administration of the currently recommended meloxicam dose (0.2 mg/kg).
	• The peak plasma concentration of meloxicam in this study was said to be similar to the peak plasma concentration achieved in clinically effective doses of meloxicam in other species (Montoya et al., 2004).
	  ○ The authors state that rabbits therefore need a much higher dose of meloxicam than 0.2 mg/kg to reach the same plasma concentration effective in other species. Further research is required to determine whether the effective plasma concentration in other species correlates to the effective plasma concentration in rabbits.

Limitations:	• Only studied the pharmacological parameter changes after 1 mg/kg meloxicam, rather than looking at the clinical impact this might have on surgical recovery time. • Although rabbits were determined to be behaviourally normal prior to the beginning of the study, the criteria used to decide this was not specified by the authors. • A small sample size was used and there was no control group. • Multiple doses of meloxicam in a 24 hour period was not considered. • Did not relate to surgical recovery time. • Breed and sex differences were not considered. • Only examined the pharmacokinetics of meloxicam in healthy animals, as clearance may have been affected in an unhealthy rabbit. • Subjective behavioural assessments by the investigator allows room for bias. • The behaviour of the animals was not filmed – as rabbits are

	prey animals, the presence of the observer may have altered their behaviour.

Goldschlager et al. (2013)	
Population:	Male New Zealand white rabbits aged between 2–3 months. Each weighed approximately 3 kg. Free from specified pathogens *Bordetella bronchiseptica*, *Salmonella* spp., cilia-associated respiratory bacillus, *Helicobacter, Encephalitozoon cuniculi, Pasteurella multocida, Pasteurella pneumotropica, Pseudomonas* spp., and hepatic and intestinal coccidiosis. The rabbits were purchased from Charles River Laboratories Inc. (Wilmington, MA) to be part of an additional study on the induction and treatment of atherosclerosis.
Sample size:	39 rabbits

Intervention details:	• Each rabbit was individually housed at between 20–23°C with 12 hours of daylight and 12 hours of darkness provided each day. They were left to acclimate to their environment for 7 days.
	  ○ The rabbits had access to ad libitum water and were fed a commercial rabbit diet.
	• Each rabbit was randomly allocated into one of four groups following a vascular cut down procedure of the femoral artery.
	  ○ Group 1 (n=10) – Given 0.03 mg/kg buprenorphine subcutaneously (SC) every 12 hours for 3 days.
	  ○ Group 2 (n=10) – Given 0.2 mg/kg meloxicam SC every 24 hours for 3 days.
	  ○ Group 3 (n=10) – Given 0.01 mg/kg buprenorphine and 1 mg/kg meloxicam SC every 24 hours for 3 days.
	  ○ Group 4 (n=9) – Given 0.5 ml of 0.5% bupivacaine locally immediately after surgery.
	• The rabbits' were weighed weekly.
	• Baseline serum biochemistry analysis was carried out prior to the study and at 7 days after the surgery.
	• Rectal swabs were taken on day 7 to assess the gut microflora.
	• Faecal samples were collected on days 0, 3, 7, 14, 21 and 28.
	  ○ Each sample collected was a pooled sample from the last 24 hours for each rabbit.
	  ○ The faecal samples were analysed for faecal corticosteroid metabolites.
	• Rabbits which displayed signs of no appetite or absent faecal production were withdrawn from the study. None of the rabbits exhibited these signs and so none were removed from the study.

Study design:	Nonblinded, parallel-group, randomised control trial
Outcome studied:	• Faecal corticosteroid metabolite (FCM) levels measured on days 0, 3, 7, 14, 21 and 28 after surgery.

	• Body weight was measured weekly. • Serum biochemistry was recorded on days 0 and 7. • Data was analysed using an Analysis of Variance (ANOVA) on Statistical Package for the Social Sciences (SPSS) software, with Huynh-Feldt corrected P values to report statistical significance. • One rabbit was excluded from analysis incorporating the FCM levels in the buprenorphine group on day 14, as data was missing.
Main findings: (relevant to PICO question):	• Groups 1, 2 and 4 all showed elevated corticosteroid metabolites in the faeces until 7 days, before then decreasing to baseline level as detected prior to the beginning of the study. • Group 3 showed unchanged faecal corticosteroid metabolite levels until treatment ceased at 3 days, at which point it began to rise. • All rabbits showed decreased food intake at day 1 postoperatively and began to return to normal baseline levels from days 7–14. However, it was not specified as to whether the food was weighed or whether this was assessed subjectively. • All groups showed a decrease in body weight, however Group 3 decreased the least. • There were no notable changes in gut microflora or haematological parameters for any of the rabbits. • Group 3 given multimodal analgesia seemed to 'mitigate postsurgical stress in rabbits' and showed the highest weight gain over the study duration, however the rise in FCM after treatment ceased suggests the duration of analgesia should be prolonged to provide adequate pain relief postoperatively. • All groups showed decreased active behaviours postoperatively. ○ The frequency of inactivity began to decrease over the 7 day postoperative period, suggesting a decrease in pain over this time. • Meloxicam administered as the sole analgesic at a dose of 0.2 mg/kg did not provide adequate pain relief compared with multimodal analgesia combining meloxicam and buprenorphine.
Limitations:	• The study only considered subcutaneous administration of meloxicam rather than oral administration. • The study used laboratory rabbits rather than pet rabbits and so this may not be fully applicable to a veterinary context. • Study assumes that increased faecal corticosteroid metabolites equates to postoperative pain in rabbits. • Behavioural assessments were made subjectively and could not have been filmed to reduce any alterations due to the presence of an observer.

	• Some of the observed effects of the surgery on the rabbit's behaviour, haematological parameters and body weight, may have been a result of the surgical procedure and not necessarily linked directly to postoperative pain.

Fredholm et al. (2013)	
Population:	8 month old, clinically normal, New Zealand white rabbits weighing between 2.41–2.89 kgs
Sample size:	Six rabbits

Intervention details:	• Each rabbit was individually housed at a temperature of 21°C with 16 hours of light and 8 hours of darkness per day.
	  ○ They were fed alfalfa pelleted food and timothy hay with access to ad libitum water.
	  ○ They were left to acclimate for 5 days and habituated to handling before the study.
	• 0.5 ml of blood was taken from either the lateral saphenous vein, cephalic vein, or auricular artery to determine baseline blood values (Haematocrit, plasma total protein, biochemistry) before meloxicam administration.
	• A physical exam was conducted and faecal samples were taken.
	• 1 mg/kg meloxicam was administered orally to each rabbit.
	• 5 ml of blood was collected at 0 (before meloxicam administration) 0.25, 0.5, 1, 2, 3, 4, 6, 8,12, 24 and 36 hours following administration.
	• A 10 day wash out period followed in which the rabbits were not given any further drugs.
	• After the 10 day washout period, 1 mg/kg meloxicam was administered every 24 hours for 5 days.
	• 5 ml of blood was collected at 0 and 4 hours post administration for the first 4 days.
	  ○ On day 5, 0.5 ml of blood was collected at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24 and 26 hours post administration.
	  ○ An additional 0.5 ml of blood was collected at the final timepoint for serum biochemistry parameter analysis.

Study design:	Descriptive, non-comparative case series

Outcome studied:	• Pharmacokinetic parameters measured:
	  ○ AUCinf.
	  ○ AUC 12–24.
	  ○ Terminal half life.
	  ○ Cmax.
	  ○ Tmax.
	  ○ Λz.
	  ○ Area under the first moment curve extrapolated to infinity.
	  ○ Mean residence time extrapolated to infinity.
	• Baseline plasma biochemical analysis and plasma biochemistry following 5 days meloxicam administration.

Main findings: (relevant to PICO question):	• There were no adverse reactions to meloxicam and no changes in the rabbit's behaviour.

	• There were no significant differences between the serum biochemistry of the rabbits before and after treatment which fell outside the 'normal' reference ranges for a rabbit.
	• 1 mg/kg of meloxicam administered orally once every 24 hours to rabbits caused higher plasma concentrations of meloxicam than the maximum plasma concentration achieved when administering meloxicam at the currently recommended oral dose (0.2 mg/kg).
	  ○ Cmax achieved here – 0.83 µg/mL.
	  ○ The Cmax in this study is similar to the Cmax achieved in dogs (0.82 µg/mL) given the clinically effective dose of meloxicam (0.2 mg/kg).
	  ○ Study suggests that therefore a higher dose of meloxicam is needed to achieve the same clinically effective plasma meloxicam concentrations as found in other species.
	• Meloxicam was found to accumulate after 5 days of receiving 1 mg/kg orally every 24 hours, so the study suggests that the dose may need to be reduced if administering for a period of time longer than 5 days.
	• The time to reaching maximum plasma concentration in this study was 6.5 hours after administration of oral meloxicam.

Limitations:	• A small sample size was used and there was no control group included. • Behaviour was used as the sole indicator of pain in the rabbits and this did not take into account potential external stressors, for example, handling stress. • The study was performed in healthy rabbits and not those undergoing surgery, which could affect drug clearance and impact adverse effects. • Sexes of the rabbits not stated. • Did not explore clinical efficacy of the given dose. • Did not explore multiple doses given in a 24 hour period.

Carpenter et al. (2009)	
Population:	8 month old, clinically normal, female New Zealand white rabbits weighing between 3.75–3.98 kg. Free from *Pasteurella* spp.
Sample size:	Eight rabbits
Intervention details:	• Rabbits were housed in indoor runs, however it was not specified whether they were housed individually or in groups or pairs. Each run contained two pet carriers to be used as 'hide' boxes. They were provided with 16 hours of light and 8 hours of darkness every 24 hours. ○ They were fed a pelleted diet and timothy hay free choice, with access to ad libitum water. • The rabbits' behaviour was subjectively assessed three times a day (mentation, attitude, food consumption, activity level, faecal production). The rabbits' were observed and it was not specified as to whether an ethogram was used.

	• Before the study, each rabbit was given a physical examination, including blood samples taken to assess PCV, total protein (TP) and a urinalysis was performed. • 2 mg/kg of meloxicam was administered orally every 24 hours to each rabbit for 10 days. • 5 ml of blood was sampled from either the lateral saphenous and cephalic vein or central ear artery at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours on days 1 and 10 after drug administration. ○ Additional samples were collected prior to meloxicam administration and 3 hours afterwards on days 3, 5 and 7 during the study.
Study design:	Descriptive, non-comparative case series

Outcome studied:	• Pharmacokinetic parameters measured.
	  ○ Area under the plasma vs time curve for the treatment period of 24 hours.
	  ○ Area under the first moment curve for the treatment period of 24 hours.
	  ○ Terminal half life.
	  ○ Cmax.
	  ○ Tmax.
	  ○ λz.
	• Changes in behaviour were assessed three times a day.

Main findings: (relevant to PICO question):	• There were no changes in mentation, activity level, faecal production or food consumption that the authors could attribute to an adverse reaction in any of the rabbits. • Drug accumulation was found to occur from day 3. • The study suggests that 0.2 mg/kg every 24 hours is a suitable dose of meloxicam to be used in rabbits. • The peak plasma concentration was reached at 6 hours post meloxicam administration. • The mean Cmax concentration reached with 0.2 mg/kg administration of meloxicam on day 10 in this study (0.24 ± 0.066 µg/ml).

Limitations:	• A small sample size was used and there was no control group.
	• The authors assumed that any behavioural changes were indicative of adverse drug reactions, and that the lack of behavioural change in these rabbits implied that there were no adverse reactions.
	• Breed, age and sex differences were not explored.
	• Subjective behavioural assessment by the investigators may have impacted the rabbit's behaviour as prey animals.
	  ○ The rabbits could have been filmed to reduce this.
	  ○ It was not specified whether the same investigator assessed all the rabbits in the study – if there were different assessors, this could result in bias.
	• The study did not assess clinical efficacy of the given dose.
	• The study was performed in healthy laboratory animals and is therefore not directly related to surgical recovery time in rabbits, or reflective of a veterinary setting.

Cooper et al. (2009)	
Population:	Female Dutch Belted rabbits all weighing between 2–3 kg were used. All rabbits were free from specified pathogens *Bordetella bronchiseptica, Salmonella* spp., *Coccidia* spp., cilia-associated respiratory bacillus, *Encephalitozoon cuniculi, Pasteurella multicoda*, and *Treponema cuniculi*. They were purchased from Myrtle's Rabbitry (Thompsons Station, TN).
Sample size:	30 rabbits (however one died from anaesthetic complications during surgery)

Intervention details:	• Each rabbit was housed individually at a temperature of 21–23°C with 12 hours of light and 12 hours of darkness each day.
	  ○ They were fed 250 g of commercial rabbit feed daily with access to ad libitum water via an automatic watering system.
	  ○ They were allowed 5–7 days to acclimate to their surroundings.
	• Baseline parameters were collected from each rabbit. These included food intake, faecal production, urine output, body weight, physical examination, complete blood count and biochemistry, rectal culture and behavioural assessment (attitude, posture, grooming, activity levels on a scale of 1–5).
	• An ovariohysterectomy was performed on each rabbit under general anaesthesia.
	• Each rabbit was randomly assigned to one of three treatment groups postoperatively.
	  ○ Group 1 (n=10) – 0.03 mg/kg buprenorphine administered via intramuscular injection every 12 hours for 48 hours.
	  ○ Group 2 (n=10) – 0.2 mg/kg meloxicam via subcutaneous injection every 24 hours for 48 hours.
	  ○ Group 3 (n=9) – 0.5 ml of 0.5% bupivacaine locally infused to the incision site after surgery.
	  ○ Any rabbit showing signs of anorexia or lack of faecal production was supplemented with 0.5 mg/kg of metoclopramide once daily for 2 days, and one handful of timothy hay.
	• Each rabbit was observed and monitored for 7 days following the procedure by a non-blinded observer.
	  ○ Pain assessment, food intake, faecal output, urine output, abdominal palpation and physical examination including the incision site was assessed.
	  ○ A complete blood count and biochemistry, weight, rectal temperature and cultures were also performed on days 2 and 5 postoperatively.

Study design:	Nonblinded, parallel group, randomised control trial
Outcome studied:	• Behavioural assessments of each rabbit postoperatively, including a pain assessment.

	• Blood sample analysis of each rabbit.
Main findings: (relevant to PICO question):	• According to this study, meloxicam appeared to be a more appropriate analgesic for use following soft tissue surgery than an opiate. • Group 2 showed the fastest return to the baseline food intake level by day 5 following surgery. • Faecal output was statistically greater in Group 2 compared with Group 3 on day 1 postsurgery (P = 0.0256), however there was no significant difference in faecal output between any of the groups after this period. • Groups 1 and 2 both showed a gradual return to baseline faecal output and food consumption by day 7. • All groups showed weight loss and reduced faecal output immediately after surgery. • Rectal culture, physical examination, blood parameters and body temperature remained similar to baseline levels throughout the study for all three groups. • Four rabbits in Group 3 showed signs of gut stasis immediately after surgery and so were treated with metoclopramide, fluids and timothy hay.
Limitations:	• Behavioural assessments were subjective and nonblinded which could have led to some bias. Again they could have been filmed to assess more natural rabbit behaviour. • Breed, sex and age differences were not considered. • The age of the rabbits was not stated. • The reduction in faecal output and gut stasis was assumed to be a direct result of pain, rather than the result of stress from the procedure, change in environment and being housed alone. • The rabbits were not fed any form of roughage and instead were only fed commercial rabbit feed. This is not reflective of an appropriate rabbit diet and therefore could have been an extra source of stress within the study. • The study administered meloxicam via subcutaneous injection rather than orally, which may be better suited to manage postoperative pain in rabbits being sent home with medications.

Leach et al. (2009)	
Population:	12 week old female New Zealand white rabbits weighing between 1.8–2.3 kg purchased from Harlan UK Limited (Bicester, UK).
Sample size:	28 rabbits

Intervention details:	• Each rabbit was individually housed at a temperature of 22°C with 12 hours of light and 12 hours of darkness each day. They were free from the common pathogens as
	• identified by the FELASA Health Monitoring Recommendations (Mähler Convenor et al., 2014).
	  ○ Rabbits were fed pellets, hay and ad libitum water.
	  ○ Cardboard tubes and a chew block were provided in

	each enclosure for enrichment. ○ The rabbits were allowed 14 days to acclimate to the surroundings prior to the study. • Each rabbit was randomly allocated into one of four groups to be given either meloxicam or a placebo orally. ○ Group 1 (n=7) – Placebo of 2 ml/kg saline on the day of surgery and for 2 days following. ○ Group 2 (n=7) – 0.2 mg/kg meloxicam on the day of the surgery and 0.1 mg/kg on the following 2 days. ○ Group 3 (n=7) – 0.6 mg/kg meloxicam on the day of the surgery and 0.3 mg/kg on the following 2 days. ○ Group 4 (n=7) – 1 mg/kg meloxicam on the day of the surgery and 0.5mg/kg on the following 2 days. • Each group received their placebo or drug dose orally one hour before the surgery, followed by doses at 09:00 for the following 2 days. • The rabbits all underwent a routine ovariohysterectomy under general anaesthesia. They were left to recover for one hour after surgery in an incubator before being returned to their individual enclosures. • Following surgery, the rabbits were monitored regularly by a veterinarian. • The rabbits were filmed at 3, 7, 27, 31, 51, 55, 75 and 79 hours postoperatively, for 20 minutes at each timepoint to monitor their behaviours. The data was recorded by a blinded observer, and an ethogram detailing the frequency and duration of each behaviour observed. • Rescue analgesia consisting of 0.01 mg/kg intravenous (IV) buprenorphine was given to any animal exhibiting two of the following behaviours in 5 minutes – abdominal writhing, belly pressing, back arching or contraction of the abdominal muscles.
Study design:	Blinded, placebo-controlled, parallel-group randomised trial
Outcome studied:	Frequency and duration of specified behaviours displayed postoperatively by the rabbits.
Main findings: (relevant to PICO question):	• Inactivity levels associated with pain increased significantly postoperatively at all timepoints ($P<0.0001$, ± 2 standard error (SE)) compared to the preoperative period with no significant difference between any of the groups. • Group 4 showed a significant difference in searching behaviour during the morning observation periods in comparison to the placebo group ($P<0.05$, ± 2 SE), being significantly higher in the high dose meloxicam group. • Groups 3 and 4 showed a significant difference in the duration of consuming behaviours ($P<0.05$ and $P<0.05$ respectively, ± 2 SE), and Group 3 showed a significant difference in the duration of interaction behaviours compared with the placebo group. • All groups showed a significant decrease in food consumption following surgery compared to before surgery ($P<0.0001$), however there was no difference between the groups. • The frequency of inactivity was significantly higher postoperatively compared to preoperatively, however did not decrease to baseline levels throughout the duration of the study (2 days postoperatively).

	• No group provided complete analgesia following ovariohysterectomy.
Limitations:	• 20 minute filming periods may not have been long enough to accurately assess the rabbit's behaviour. • The study assumed that inactivity levels were associated with pain rather than stress. • No sex, age or breed differences were considered.

Turner et al. (2006)	
Population:	3 month old, female, New Zealand white rabbits, all weighed approximately 3 kg. All rabbits were free from specified diseases *Encephalitozoon cuniculi*, cilia-associated respiratory bacillus, *Clostridium piliforme*, reovirus, rotavirus, *Pasteurella multocida, Salmonella spp, Bordetella bronchiseptica, Pseudomonas aeruginosa, Clostridium perfringens*, and hepatic and intestinal coccidiosis. They were obtained from Charles River Canada.
Sample size:	10 rabbits

Intervention details:	• The rabbits were housed in a group in floor pens with 12 hours light and 12 hours of darkness a day, at a temperature of 20°C.
	  ○ Rabbits were fed twice a day with a commercial diet and provided with timothy hay and water ad libitum.
	  ○ The rabbits were given 7 days to acclimate to the conditions and were habituated to handling prior to the study taking place.
	• Each rabbit was randomly allocated to one of two initial treatment groups to be given a single dose of oral meloxicam.
	  ○ Group 1 (n=5) – 0.3 mg/kg meloxicam orally at 08:00.
	  ○ Group 2 (n=5) – 1.5 mg/kg meloxicam orally at 08:00.
	• A 1 ml blood sample was collected from each rabbit at 0, 0.5, 1, 2, 4, 6, 8, 24, 48, 72 and 96 hours following administration of the single meloxicam dose.
	  ○ There was a wash-out period of 14 days following.
	• After the wash out period, the rabbits were then allocated to one of two repeat dose groups.
	  ○ Group 1 from the single dose study (receiving 0.3 mg/kg meloxicam) was now given 1.5 mg/kg oral meloxicam each day for 5 days.
	  ○ Group 2 from the single dose study (receiving 1.5 mg/kg meloxicam) was given 0.3 mg/kg oral meloxicam for 5 days.
	• A 1 ml blood sample was collected from each rabbit at 0, 4, 24, 28, 48, 96, 100, 120 and 144 hours after dosing.
	• The body weight of each rabbit was measured each week.
	• Baseline blood biochemistry parameters were measured before the study, and at 5 days following both the single and repeat dose experiments.

Study design:	Randomised crossover trial

Outcome studied:	• Plasma meloxicam levels and time to reaching peak plasma concentration were measured.
	• Body weight was recorded weekly.
	• Biochemical parameters were established at baseline and 5 days post administration of both the single and multiple dose studies.
	• Pharmacokinetic parameters were calculated.
	  ○ Elimination constant.
	  ○ Plasma concentration-time curve.
	  ○ AUC.
	  ○ Oral clearance.

Main findings: (relevant to PICO question):	• There was no significant change in body weight or biochemical parameters for either group in either study. • The maximum plasma concentration of meloxicam for 0.3 mg/kg and 1.5 mg/kg single daily dosing was reached between 6–8 hours and decreased to untraceable levels by 24 hours (0.025 ± 0.06 µg/ml and 0.069 ± 0.021 µg/ml for Group 1 and 2 respectively). • The elimination half-life was 8 hours for both doses, implying no saturation as the dose was increased to 1.5 mg/kg. • The repeated dose experiments showed little evidence of accumulation at either dose given for 5 consecutive days, with meloxicam eliminated quickly after dosing ceased. • The plasma meloxicam levels after 4 hours on days 1, 2 and 4 following meloxicam administration were similar for both doses in the repeated and single dose studies. • There was some individual variation between the maximum plasma concentration in each rabbit. • The peak plasma concentration of meloxicam reached in this study (0.14 ± 0.02 µg/ml and 0.30 ± 0.09 µg/ml for the low and high dose groups respectively) was much lower than the maximum plasma concentration reached in other species, using the same dose of meloxicam (e.g. 0.0464 µg/ml in Beagle dogs after a dose of 0.2 mg/kg) – this was hypothesised to be as a result of poor drug absorption rather than over-saturation. • The study hypothesises that feeding food and roughage prior to meloxicam administration can slow the absorption of oral meloxicam. • 3 mg/kg and 1.5 mg/kg were both determined to be clinically safe doses in rabbits. • The oral clearance and volume of distribution increased from the low to high dose groups, again hypothesised here to be a result of poor absorption. • This study suggests that meloxicam is metabolised faster in rabbits than in other species e.g. humans, rats and dogs and further studies are needed to assess the effective plasma concentration of meloxicam in rabbits.

Limitations:	• Breed, gender and age differences were not considered. • The clinical efficacy of either dose was not considered. • The study was conducted in healthy rabbits and so it is possible the metabolism and clinical efficacy of meloxicam could be different in a sick animal. • No behavioural effects of the drug were monitored or measured throughout either study.

Raillard et al. (2019)	
Population:	17 week old, male New Zealand white rabbits obtained from Charles River Laboratories, France
Sample size:	14 rabbits

Intervention details:	• Each rabbit was individually housed with 12 hours of light and 12 hours of darkness each day, at a temperature of between 19–21°C.
	  ○ The rabbits maintained visual contact with each other as the space between two enclosures was left open.
	  ○ If there was any aggression, a transparent partition was placed between enclosures.
	  ○ A wooden block, chew ball and elevated level was provided in each enclosure for enrichment.
	  ○ The rabbits were left to acclimate for 3 weeks prior to the study.
	  ○ They were fed 200 g of commercial rabbit food with ad libitum water each day.
	• The rabbits were anesthetised, and calvarial bone surgery was performed on each rabbit.
	• Postoperative pain was monitored and assessed using the composite behavioural scale and RbtGS (Keating et al., 2012).
	  ○ Baseline pain scores were assessed 3 days before surgery.
	  ○ Postoperative pain was assessed before drug administration by one of three trained persons at 06:00, 10:00, 14:00, 18:00 and 22:00 on the day of surgery and for 3 days following.
	• 3 mg/kg meloxicam was given via subcutaneous injection once daily for 4 days, and 20–30 mcg/kg buprenorphine was given three times daily (06:00, 14:00 and 22:00) via subcutaneous injection for 3 days after surgery.
	  ○ Rescue analgesia consisting of 20–30 mcg/kg buprenorphine SC was given at 10:00 and 18:00 if a score higher than 3 on the composite pain scales, or higher than 4 on the RbtGS was reached.

Study design:	Nonblinded, descriptive non-comparative case series
Outcome studied:	Postoperative pain assessments were obtained.
Main findings: (relevant to PICO question):	• Postoperative pain was observed in every rabbit despite the administration of multimodal analgesia.

	• The peak pain levels were reached at 12 hours following surgery and on the first day after surgery. • Every rabbit required analgesia every 4–8 hours on the day of the surgery and for 1 day following surgery. • The study suggests that rigorous pain monitoring is required postoperatively in rabbits and that analgesia should be administered for at least 48 hours after any surgical procedure.
Limitations:	• Breed, age and sex differences were not considered. • The study did not account for the stress that might have been associated with the change in environment for the rabbits and did not consider whether they were used to living alone or in pairs. This could have increased stress levels and been mistaken for increased pain levels postsurgery. • The rabbits were not fed any form of roughage which is not representative of an appropriate rabbit diet and therefore could have acted as an extra cause of stress during the study. • Increasing the dose of meloxicam was not considered. • The study did not consider directly comparing the efficacy of different postoperative analgesic protocols. • The observers were not blinded, leaving room for some bias. • There was no control group to compare against. • The presence of the observers could have affected the display of pain behaviour and the behaviour of the rabbits could have been filmed to eliminate bias.

Appraisal, application and reflection

Much of the literature reviewed here agrees that a dose exceeding the currently recommended 0.2–0.3 mg/kg/day is required to provide adequate analgesia for rabbits postoperatively. These papers consisted of one nonblinded, randomised control trial (Cooper et al., 2009); two descriptive case series' (Delk et al., 2014; and Fredholm et al., 2013); one blinded, placebo-controlled, parallel-group, randomised trial (Leach et al., 2009) and one randomised crossover trial (Turner et al., 2006). Despite their concordance, the strength of the evidence remains weak pertaining to the PICO question asked in this Knowledge Summary. None of the papers consider dosing with meloxicam twice daily, and not all the studies assess postoperative pain behaviours directly. Leach et al. (2009) conducted a blinded randomised control trial assessing postoperative behaviour of rabbits following ovariohysterectomy. This is perhaps the most directly relevant paper to the PICO in this sense, especially as it considers increasing the daily doses of meloxicam in a surgical context, yet it again fails to consider dosing twice a day. The study found that inactivity behaviours increased following surgery, and only the higher dose group showed an increase in searching and consuming after surgery. Despite this, the increased searching and consuming behaviours were only significant in the morning observation periods and none of the meloxicam groups provided adequate analgesia postoperatively, even up to a dose of 0.6 mg/kg/day, again suggesting an increased dose is necessary. It is important to note, however, that each study used different, subjective criteria to assess pain and so there is scope for variation amongst what was deemed to be 'painful' in each study. Fredholm et al. (2013) and Delk et al. (2014) examined the pharmacokinetics of meloxicam in rabbits. Both concluded that the peak plasma concentration of meloxicam in rabbits given 1 mg/kg orally was much higher than that reached when 0.2 mg/kg was administered (Carpenter et al., 2009). As the rabbit metabolism is very fast, this could mean that higher doses are required to maintain a higher plasma concentration of the drug and provide adequate pain relief, although the study did not examine the

significance of the relationship between plasma concentration and clinical efficacy. Again, the plasma concentration reached with 1 mg/kg of meloxicam was much closer to the plasma concentration reached with the clinically effective doses of meloxicam in other species (Delk et al., 2014), implying that a higher concentration is required to be clinically effective in rabbits. However, this was not directly assessed in this paper and instead assumes that a higher plasma concentration equals clinical effectiveness, leaving scope for future research to be undertaken here.

Carpenter et al. (2009) and Cooper et al. (2009) both imply that 0.2 mg/mg of meloxicam is an adequate dose for rabbits in their studies, contradicting the previous findings. However, Cooper et al. (2009) conducted a randomised control trial and found that whilst 0.2 mg/kg meloxicam allowed a faster return to baseline levels following ovariohysterectomy, all rabbits still showed decreased activity and faecal output levels immediately after surgery. This may suggest that either a higher daily dose, or a lower dose given more frequently, may be necessary to provide adequate analgesia postoperatively. Again, the strength of the evidence provided by Cooper et al. (2009) in their nonblinded, parallel group control trial is much greater than Carpenter et al. (2009) in their descriptive case series, perhaps giving more credibility to their conclusions.

Some sources concluded that there are no adverse side effects associated with an increased dose of meloxicam (Turner et al., 2006; Delk et al., 2014; and Eshar & Weese, 2014). These studies assessed meloxicam concentrations between 1–1.5 mg/kg/day, each finding that there were no behavioural changes or alterations in the gut microbiome following administration of this increased dose. As two descriptive case series' and one randomised crossover trial, they provide moderate evidence suggesting that there are minimal associated side effects with increased meloxicam concentrations in rabbits. However, these studies were conducted on healthy animals, rather than those recovering from surgery, therefore are not directly relevant to the PICO Contrary to this, Carpenter et al. (2009) and Fredholm et al. (2013) both found some level of drug accumulation following meloxicam administration for 3 and 5 days respectively. Drug accumulation occurs when the repeated administration of a drug results in gradually higher plasma concentrations than the first time a drug is administered, often leading to toxic side effects (Wagner, 1967). In meloxicam in dogs, these toxic side effects include renal, hepatic and gastrointestinal toxicity (Boehringer Ingelheim, 2014). Therefore, further investigation of this is needed to determine a safe clinical dose with minimal risk of drug accumulation. Carpenter et al. (2009) only considered meloxicam administration at 0.2 mg/kg/day and instead suggests that this is a suitable dose for rabbits, despite the evidence of accumulation at days 3 and 5. Fredholm et al. (2013) instead found accumulation after 5 days of 1 mg/kg administration of meloxicam and suggested that a decrease in drug concentration may be necessary. The suspected accumulation of meloxicam at this higher dose of 1 mg/kg suggests that this PICO question warrants further investigation into whether lower doses of meloxicam administered more frequently, such as twice daily, are needed to provide adequate pain relief and minimise the risk of drug accumulation. Carpenter et al. (2009) also assumed that a lack of behavioural changes indicated that there were no adverse reactions to this dose of meloxicam. Whilst a loss of appetite could indicate an adverse reaction, other factors, such as diarrhoea, were not considered, therefore limiting the value of this study further. Both studies were descriptive case series' with no comparative control group and therefore cannot provide strong enough evidence to draw reliable conclusions. Each paper studied only one age and breed of rabbit, using heavily controlled environments and the results, therefore, are less applicable to a real-life veterinary scenario involving pet rabbits. However, each of these papers provide a useful starting point for future research into this topic.

As previously discussed, there were no directly relevant papers comparing the effects of twice daily meloxicam administration with single daily dosing. Instead, it is only possible to extrapolate data from the existing available literature. Again, each of the studies examined in this Knowledge Summary used only laboratory rabbits, rather than pet rabbits. Most of these animals were housed individually, rather than in groups, which is unacceptable according to the Animal Welfare Act, 2006 (Legislation.gov.uk, 2006). These conditions are not fully reflective of a veterinary context and could have provided an extra source of stress to the rabbits, further influencing their behaviour and the interpretation of study results. Whilst these studies do not provide enough basis on which to build any solid conclusions, they point in the direction of future research which is most

certainly required to ascertain a reliable answer to the clinical query asked here, and to allow veterinarians to provide the best possible postoperative care to their patients. It is therefore vital that additional research is conducted that accounts for other external stressors such as poor diets, housing and the threat of predation if kept outside, to allow for appropriate assessment of pain relief in domestic rabbits.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts via Ovid 1973 – 2021 PubMed via NCBI 1948 – 2021
Search terms:	CAB Abstracts: 1. Rabbit* OR leporid* OR lagomorph* OR lapine OR Oryctolagus* AND 2. Meloxicam OR Metacam OR MLX OR Loxicom OR Meloxidyl OR nonsteroidal OR non-steroidal OR "non steroidal" OR NSAID OR analgesi* AND 3. Dose* OR dosing OR dosage* OR inject* OR administ* *Filters applied: English* PubMed: (((rabbit OR lapine OR lagomorph OR rabbits OR oryctolagus)) AND (Meloxicam OR Metacam OR MLX OR nonsteroidal OR non-steroidal OR "non steroidal" OR NSAID OR analgesia))) AND ((dose OR doses OR dosing OR dosage OR inject OR administer OR administration)) *Filters applied: English, Other Animals, Veterinary*
Dates searches performed:	29 Mar 2021

Exclusion / Inclusion Criteria	
Exclusion:	Review articles, not in English, book or book chapters, not relevant to PICO, dose charts, opinion articles, inability to access full paper
Inclusion:	Articles relevant to PICO

Search Outcome				
Database	**Number of results**	**Excluded – Irrelevant to PICO**	**Excluded – Review paper/book chapters/inability to access etc.**	**Total relevant papers**
CAB Abs	222	189	24	9
PubMed	698	679	10	9
Total relevant papers when duplicates removed				**9**

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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