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Toxic Effects of High-dose Meloxicam and Carprofen on Female CD1 Mice

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The nonsteroidal anti-inflammatory drugs meloxicam and carprofen are commonly used as analgesics in mice. The current recommended doses of meloxicam at 0.2-1.0 mg/kg once daily and carprofen at 5-10 mg/kg twice daily may not be adequate to provide analgesia in mice. Several studies have suggested that doses up to 20 mg/kg of meloxicam and carprofen are needed to provide analgesic efficacy. This study investigated the clinical safety of these higher doses of meloxicam and carprofen by evaluating their potential for renal and gastrointestinal toxicity. Female CD-1 mice were given 20 mg/kg of either meloxicam, carprofen, or an equivalent volume of saline subcutaneously once daily for 3 or 7 d. On day 4, mice treated for 3 d were euthanized, and on days 8 and 15, mice treated for 7 d were euthanized. Blood was collected by cardiocentesis for serum chemistry analysis. Feces was collected from the colon for fecal occult blood testing, and tissues were collected for histopathology. No clinically significant changes in serum chemistry profiles were found in the drug-treated mice at any time point as compared with the saline controls. Fecal occult blood and histologic evidence of gastritis was associated with meloxicam administration in mice evaluated at days 4 and 8. By day 15, there was no association with meloxicam treatment and the presence of fecal occult blood or gastritis. There was no association between fecal occult blood and gastritis in the carprofen or saline-treated mice regardless of the treatment durations. These findings suggest that 20 mg/kg of meloxicam in mice causes gastric toxicity when given for 3 or 7 d and should be used cautiously; however, carprofen at 20 mg/kg appears to have minimal toxic effects with regard to the parameters measured.

Abbreviations: Alb, Albumin; Chol, cholesterol; CK, creatine kinase; COX, cyclooxygenase; Glob, globulin; Glu, glucose; NSAIDS, nonsteroidal antiinflammatory drugs; PG, prostaglandinTB; total bilirubin; TP, total protein

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Introduction

Arachidonic acid is released from damaged cells, initiating a cascade of inflammatory mediators through prostaglandin (PG) production catalyzed by cyclooxygenases (COX).[2,21,26] The PG sensitizes nociceptive nerves,[2] enhancing the pain response. Nonsteroidal anti-inflammatory drugs (NSAIDS) exert their effect on this cascade by inhibiting the COX production of PGs.[9] The known isoforms of COX are COX-1 and COX-2. COX-1 catalyzes the production of PGs that are integral to normal physiologic functions such as protection of the gastric mucosa and normal clotting, whereas COX-2 produces PG that is associated with inflammation.[2,14,21] COX-1 inhibition of PG synthesis is frequently associated with the toxic side effects of NSAIDS, whereas COX-2 is selective for anti-inflammatory effects with fewer toxic side effects of NSAIDS.[2,14]

Meloxicam and carprofen have greater inhibition of COX-2 activity as compared with their COX-1 activity, and hence are primarily anti-inflammatory.[2,14] Both drugs are commonly used to provide analgesia in mice, as they reduce inflammation and inflammatory mediators that activate peripheral nerves.[17,21] Several reports suggest that the commonly used dosages of meloxicam and carprofen may be too low to produce analgesia.[15,16,20,29] For example, on one study male CD1 mice were vasectomized and treated with 5 mg/kg meloxicam, and analgesia was evaluated based on behavioral changes.[16] No significant differences in the behavioral changes were found following the meloxicam treatment compared to their baseline observations, suggesting that the dosage was ineffective.[16] When higher doses of meloxicam (5, 10, or 20 mg/kg) were evaluated in male C57BL/6JCrl and C3H/HeN mice after a midline laparotomy, those treated with the 20 mg/kg dose had lower fecal corticosterone values than those treated with 5 or 10 mg/kg, suggesting an improved analgesic effect.[29] Similar findings were reported in female mice treated with carprofen.[11] After a sham embryo transfer surgery, female C57BL/6J mice were treated with 5 or 50 mg/kg of carprofen, and their responses were assessed using a nest complexity score.[11] Mice treated with the higher dose had a slight improvement in nest complexity, and the low dose had no effect.[11] Similarly, female outbred mice treated with carprofen at 5, 10, 15, 20, and 25 mg/kg after a midline laparotomy procedure were evaluated using the mouse grimace scale.[15] A reduction in the mean mouse grimace score was observed only with the highest doses of carprofen (20 and 25 mg/kg).[15]

The pharmacokinetic profile of meloxicam and carprofen at commonly used doses also suggests that the frequency of dosing may not be adequate.[12] Meloxicam administered at 1 mg/kg SC maintained therapeutic levels for 4 to 8 h, and carprofen administered at 5 mg/kg SC maintained therapeutic levels for 8 to 12 h.[12] Higher initial doses may result in prolonged therapeutic levels. Together, these findings suggest higher and more frequent doses of NSAIDS are necessary, prompting recent publications to suggest the use of higher doses.[4-6] However, these higher doses approach ulcerogenic doses in mice.[5,13]

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The aim of this study was to evaluate the toxic effects of high-dose meloxicam and carprofen in CD1 female mice. Our study investigated the clinical safety of higher doses of meloxicam and carprofen by evaluating their potential for renal and gastrointestinal toxicity Mice were given daily treatments of high-dose (20 mg/kg) meloxicam or carprofen subcutaneously for 3 or 7 d. Serum chemistry was performed to assess organ function and toxicity. Fecal occult blood tests were performed to identify blood in the feces, and histology was performed on major organs. Gastrointestinal toxicity was present in mice that received high-dose meloxicam and was most pronounced after 7 consecutive days of treatment, whereas toxicity associated with carprofen was minimal. These results suggest that high-dose meloxicam should be used with caution, whereas high-dose carprofen may be safe.

Materials and Methods

Mice. Female Crl:CD1(ICR) female mice (n = 54) ranging in weight from 24 to 40 g and 6 to 8 wk of age were obtained from Charles River Laboratories (Wilmington, MA). Based on vendor reports, mice were free of Sendai virus, mouse hepatitis virus, minute mouse virus, mouse parvovirus, mouse norovirus, Theiler murine encephalitis virus, rotavirus, *Mycoplasma pulmonis*, pinworms, and ectoparasites. Mice were housed in individually ventilated cages (Thoren #9 to 19.56 cm × 30.91 cm × 13.34 cm, Thorne Caging Systems, Hazleton, PA) with Sani-Chip bedding (Tekald 7090, Envigo, Madison, WI). Mice had ad libitum access to Teklad Irradiated Diet 2918 (Envigo, Madison, WI) and filter-sterilized water. Mice were maintained on a 14:10-h light: dark cycle at a temperature of 21 to 24 °C (17-75°F). Mice were acclimated to these conditions for at least 7 d prior to experimental use. All experimental procedures were approved by the Institutional Animal Care and Use Committee.

NSAID treatment. Individual mice were randomly assigned to one of 3 treatment groups to provide 6 mice per treatment and for a total of 54 mice. Each treatment group had 3 time points. To maintain social housing, mice were housed 3 per cage. The cage assignments were separate from the treatment assignment, such that a cage may include mice from one to 3 treatment groups (although no cage had more than 2 mice in a single treatment group). Each mouse in a cage is effectively independent for the parameters that were measured. Mice were treated with either meloxicam at 20 mg/kg (5 mg/mL, Boehringer Ingelheim, Ridgefield, CT), carprofen at 20 mg/kg (50 mg/mL (diluted to 5 mg/mL in saline), Rimadyl injectable, Zoetis, Kalamazoo, MI), or equivalent volume of 0.9% saline treatment based on the meloxicam dose (0.9% Baxter Health Care, Deerfield, IL). Mice were manually restrained by scruffing the head and neck and holding the tail for subcutaneous injection in the inguinal region every 24 h. One cohort of mice was dosed for 3 d and euthanized at day 4 (n = 6 per group). One cohort of mice was dosed for 7 d and euthanized at day 8 (n = 6 per group) and another dosed for 7 d was allowed a week recovery, then euthanized at day 15 (n = 6 per group). Mice were euthanized by carbon dioxide asphyxiation.

Toxicity assessment. Blood was collected after euthanasia by cardiocentesis and placed in a red top microtainer tube (Becton Dickinson, Frnaklin Lakes, NJ). Serum was separated by centrifugation at 3500g for 10 min and submitted to the Colorado State University Veterinary Diagnostic Laboratory (CSU-VDL) for serum chemistry assays (glucose, BUN, create, P, Ca, TP, Alb, Glob, Chol, CK, TB, ALP, ALT, AST, Na, K, Cl, and HCO3). Feces was collected at necropsy from the colon for fecal occult blood analysis (Hemoccult, Beckman Coulter, Bree, CA).[7,23] One fecal pellet was placed in a 1.5 mL microfuge tube with 1.0 mL sterile PBS. The fecal pellet was mixed with the PBS and smeared on the fecal occult paper according to the manufacturer's instructions. Three days later, the assay was read; positive fecal occult blood was indicated by a blue color change in the paper. Tissues including liver, spleen, kidney, heart, lung, stomach, duodenum, ileum, cecum, and colon were collected for histopathology and fixed in 10% neutral buffered formalin formaldehyde. Tissues were paraffin-embedded, and 5µm sections were applied to glass slides and stained with hematoxylin and eosin for routine histopathologic analysis. Lesions at the pyloric-duodenal junction were scored on a scale of 0 to 4 by a pathologist who was blind to the treatment groups as follows: 0- no significant lesions; 1- mild gastritis characterized by mild neutrophilic infiltrates; 2- mild gastritis characterized by mild neutrophilic infiltrates and mild mucosal ulcerations; 3- moderate gastritis with mucosal ulceration; 4- marked gastritis with mucosal ulceration.

Statistical analysis. Six mice were used per time point and treatment group based on previous studies.[22] Descriptive values are presented as the mean with standard deviations. Data analysis was performed using Prism 8.0.2 (GraphPad Software, San Diego, CA). Serum chemistry tests were analyzed for normality. A one-way ANOVA was performed on those analytes that were normally distributed (Glu, BUN, Ca, ALP, HCO3) with a Sidak's multiple comparison test to compare the treatment groups at each time point, and a Kruskal-Wallis test for analytes that were not normally distributed (create, P, TP, Alb, Glob, Chol, CK, TB, ALT, AST, Na, K, Cl) with a Dunn's multiple comparison test to compare the treatment groups at each time point. Analytes were compared with the saline treatment at the same time point. Fecal occult blood results were compared between treatment groups for each day using a Freeman-Halton extension of the Fisher's exact test. Histologic scores of gastritis were compared with the saline treatment at the same time point using a Kruskal-Wallis test. Gastritis scores were compared between treatment groups on each day using a Freeman-Halton extension of the Fisher's exact test. A Fisher's exact test was used to assess the association between the fecal occult blood and the histologic evidence of gastritis. For all tests, $P < 0.05$ was considered statistically significant.

Results

Female CD-1 mice were given 20 mg/kg meloxicam or carprofen, or an equivalent volume of saline daily for 3 or 7 d. With the exception of a few mice having bruising at the injection site in the 7-d dosing groups, all mice appeared healthy at the time of euthanasia. Table 1 provides an overview of the serum chemistry results and Table 2 provides individual fecal occult blood and gastritis scores for each treatment group.

On day 4, the 6 mice from each of the 3-d treatment groups were euthanized and samples collected for analysis. Meloxicam-treated mice had lower albumin and higher globulin concentrations as compared with both carprofen (P = 0.007 and 0.003) and saline-treated mice (P = 0.04 and 0.01, Table 1). Meloxicam-treated mice also had significantly lower ALP concentrations as compared with carprofen-treated mice (P = 0.02). No other significant changes in serum chemistry values were detected on day 4. On day 4, fecal occult blood was present in 3 of 6 meloxicam, 0 of 6 carprofen, and 1 of 6 saline-treated mice. The presence of fecal occult blood had a weak association with the treatment (P = 0.11). The mean gastritis score in the meloxicam treated group was higher than the carprofen (P = 0.02) and saline-treated groups (P = 0.09, Figures 1 and 2). No significant lesions were noted in the other tissues examined.

Table 1. Serum chemistry values of mice following high-dose meloxicam and carprofen.

Day	4			8			15		
Treatment Group	**Melox**	**Carp**	**Sal**	**Melox**	**Carp**	**Sal**	**Melox**	**Carp**	**Sal**
Glucose (mg/dL)	297(53)	308(55)	322(77)	330(62)	297(64)	274(74)	290(66)	251(24)	267(74)
BUN (mg/dL)	16.8(2.8)	18.8(3.4)	17.5(2.4)	16(2.8)	17.7(3.2)	15.8(3.3)	22.4(4.2)	19.4(3.3)	22.7(3.6)
Creatinine (mg/dL)	0.2(0.05)	0.2(0.05)	0.2(0.05)	0.2(0.05)	0.2(0.4)	0.2(0)	0.2(0.05)	0.2(0.05)	0.2(0.05)
Phos (mg/dL)	10.3(4.7)	12.4(1.3)	11.9(1.1)	12.4(1.2)	11.2(0.9)	12.8(1.4)	13.0(0.5)	13.4(0.7)	12.5(0.9)
Ca (mg/dL)	11.7(0.3)	11.7(0.4)	10.9(0.5)	11.6(0.5)	11.1(0.4)	11(0.4)	11.4(0.3)	11.1(0.1)	11.3(0.3)
TP (g/dL)	5.3(0.5)	5.8(0.2)	5.6(0.4)	5.4(0.3)	5.5(0.3)	5.9(0.2)	5.7(0.2)	5.8(0.2)	5.8(0.2)
Alb (g/dL)	3.5(0.6)[a,b]	4.2(0.1)	4.0(0.2)	3.7(0.3)	4.1(0.1)	4.2(0.1)	4.1(0.3)	4.2(0.2)	4.2(0.2)
Glob (g/dL)	2.0(0.2)[a,b]	1.6(0.1)	1.6(0.3)	1.7(0.1)[a]	1.4(0.2)	1.6(0.1)	1.6(0.2)	1.6(0.1)	1.5(0.1)
Chol (mg/dL)	185(57)	165(11)	151(30)	141(18)	119(14)	140(24)	146(30)	140(24)	140(14)
CK (IU/L)	197(150)	437(611)	169(138)	130(99)	187(111)	551(516)	522(449)	824(245)	574(521)
T. bili (mg/dL)	0.14(0.1)	0.1(0)	0.12(0.4)	0.1(0)	0.13(0.08)	0.12(0.04)	0.1(0)	0.1(0)	0.1(0)
ALP (IU/L)	95(41)a	157(30)	144(21)	88(40)	121(16)	140(25)	105(34)	129(14)	118(19)
ALT (IU/L)	45(32)	33(11)	69(63)	26(11)	59(62)	38(17)	50(29)	57(18)	106(108)
AST (IU/L)	95(50)	128(114)	131(141)	65(17)	148(110)	181(102)	120(35)	227(34)	236(147)
Na (mEQ/L)	148(3)	148(3)	148(2)	152(2)	152(3)	152(1)	154(0.4)	154(1)	152(1)
K (mEQ/L)	13(1)	12(1)	13(3)	13(1)	12(1)	11(1)	12(1)	12(1)	12(1)
Cl (mEQ/L)	106(3)	105(4)	106(2)	113(1)	112(3)	112(1)	112(2)	113(2)	112(2)
HCO3 (mEQ/L)	19.6(0.9)	19.8(1.7)	19.5(3.4)	20.0(2.1)	21.2(2.1)	18.9(4.7)	18.6(1.8)	17.5(0.7)	17.8(2.1)

Values presented as mean (standard deviation).
[a]- statistically significant difference compared with carprofen.
[b]- statistically significant difference compared with saline.

Table 2. Fecal occult blood and histologic gastritis scores of mice treated with high-dose meloxicam and carprofen.

Day	4			8			15		
Treatment	**Mouse ID**	**FOB**	**Gastritis**	**Mouse ID**	**FOB**	**Gastritis**	**Mouse ID**	**FOB**	**Gastritis**
Meloxicam	1	+	3	7	+	1	13	–	0
	2	–	0	8	+	1	14	–	0
	3	–	3	9	–	0	15	–	0
	4	–	1	10	+	0	16	–	0
	5	+	0	11	+	2	17	–	0
	6	+	1	12	+	4	18	+	0
	Summary	3/6	1.3 (1.3)*		5/6	1.3 (1.5)		1/6	0 (0)
Carprofen	1	+	0	7	–	0	13	+	0
	2	–	0	8	–	0	14	–	1
	3	–	0	9	–	1	15	–	0
	4	–	0	10	–	0	16	–	0
	5	–	0	11	–	0	17	–	0
	6	–	0	12	–	0	18	–	0
	Summary	1/6	0 (0)		0/6	0.2 (0.5)		1/6	0.2 (0.5)
Saline	1	–	0	7	–	0	13	–	0
	2	–	0	8	–	0	14	–	0
	3	–	0	9	–	0	15	–	0
	4	–	0	10	–	0	16	–	0
	5	–	1	11	–	0	17	–	0
	6	–	0	12	+	0	18	–	1
	Summary	0/6	0.2 (0.5)		1/6	0 (0)		0/6	0.2 (0.5)

FOB- fecal occult blood. Gastritis summary provides the mean (SD).
* statistically significant increase compared with carprofen.

On day 8, 6 mice from each of the 7-d treatment groups were euthanized and samples were collected for analysis. Meloxicam-treated mice had a significantly lower globulin concentration than did carprofen-treated mice ($P = 0.04$). No other significant changes in serum chemistry values were detected on day 8. On day 8, fecal occult blood was present in 5 of 6 meloxicam, 0 of 6 carprofen, and 1 of 6 saline-treated mice. The presence of fecal occult blood was associated with the treatment ($P = 0.005$) The presence of gastritis was not different between the meloxicam group and carprofen ($P = 0.1$) and saline-treated groups ($P = 0.1$, Figures 1 and 2). No significant lesions were detected in the other tissues examined.

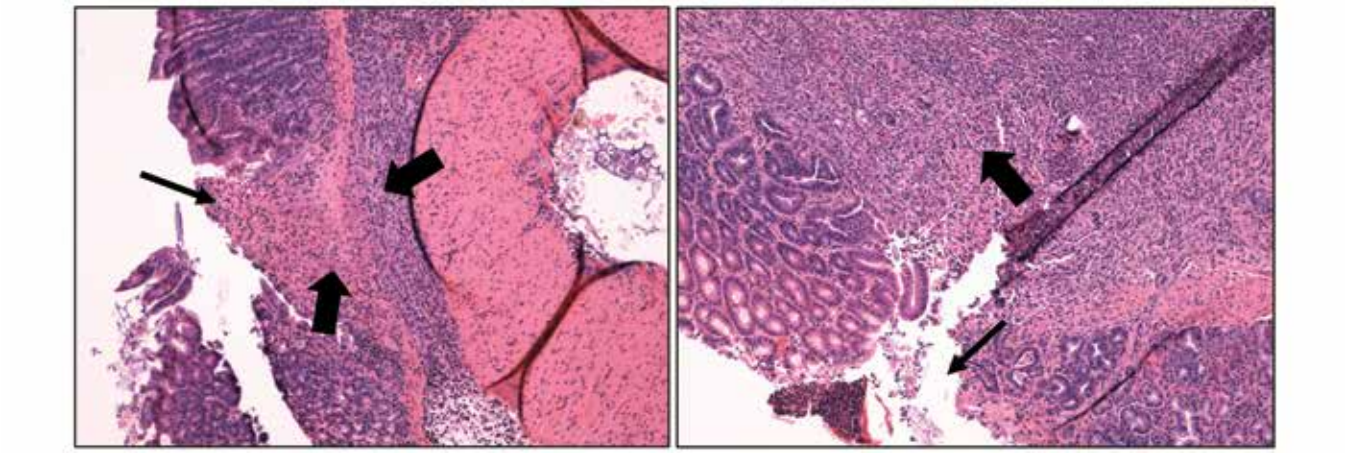

Figure 1. Histologic section from the pyloric-duodenal junction of meloxicam treated mice demonstrating areas of ulceration (arrow) with submucosal and mucosal inflammatory cell infiltrates (wide arrow). A- 10×; B- 40 × .

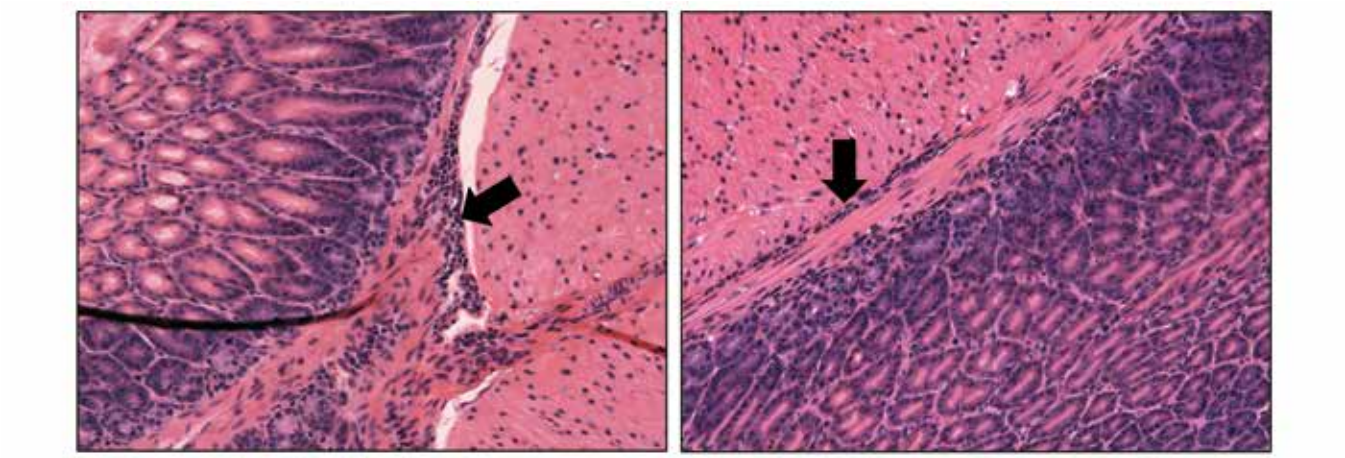

Figure 2. Histologic section from the pyloric-duodenal junction of carprofen (A) and saline (B) treated mice demonstrating areas of mild submucosal inflammatory cell infiltrates (arrow). 10 × .

On day 15, after a drug-free week for recovery, 6 mice from each of the 7-d treatment groups were euthanized and samples were collected for analysis. No changes in serum chemistry values were observed among groups on at day 15. On day 15, fecal occult blood was present in 1 of 6 meloxicam, 1 of 6 carprofen, and 0 of 6 saline-treated mice. The presence of fecal occult blood was not associated with the treatment ($P = 0.6$). Gastritis was not present in the meloxicam-treated mice, while 1 of 6 carprofen and 1 of 6 saline-treated mice had mild gastritis. The gastritis scores were not significantly different between the groups ($P = 0.7$). No significant lesions were detected in the other tissues examined.

The meloxicam-treated mice had higher gastritis scores on day 4 ($P = 0.06$) and day 8 ($P = 0.06$) of treatment as compared with day 15 (Table 2). The carprofen and saline-treated mice had no significant differences in gastritis scores over time. An association between the presence of fecal occult blood and histologic evidence of gastritis was present across all time points and groups ($P = 0.02$). Positive fecal occult blood was found in 6 of 12 mice with histological gastritis and in 6 of 42 mice without gastritis (Table 2). The presence of fecal occult blood ($P = 0.002$) and gastritis ($P = 0.01$) were also associated within treatment group. Positive fecal occult blood was found in 9 of 18 meloxicam, 2 of 18 carprofen, and 1 of 18 saline-treated mice. Similarly, gastritis was found in 9 of 18 meloxicam, 2 of 18 carprofen, and 2 of 18 saline-treated mice (Table 2).

Discussion

Improved pain management is an important goal in the experimental use of rodents, and several recent publications have suggested that higher doses of NSAIDS may be necessary to provide adequate analgesia for mice.[4,6,15,16,29] The most common toxicities associated with NSAIDS are gastric ulcers and hemorrhage, renal toxicity, and platelet dysfunction.[2,3,13] In this study, we evaluated the potential toxic effects of high-dose meloxicam and carprofen in female mice. Analgesic dosing regimens vary widely, and we chose to assess the toxicity after 3 d of treatment as a proxy for short-term analgesia, and 7 d of treatment as a proxy for long-term analgesia. To assess possible long-term effects, mice treated for 7 d were given a week to recover before euthanasia. Fecal occult blood and gastritis were found more frequently in the meloxicam treated mice after a 3- or 7-d dosing regimen than in the carprofen- and saline-treated mice. Mice that were treated for 7 d and given a week to recover had no evidence of gastritis in any treatment group, suggesting the meloxicam-induced lesions had resolved after treatment ceased. No evidence of renal or hepatotoxicity was detected in either the meloxicam or carprofen treated mice at any time point.

Meloxicam and carprofen are selective COX-2 inhibitors and have a greater influence on inhibiting prostaglandin production in the inflammatory pathway than on the physiologic pathway that maintains gastrointestinal protection, renal blood flow, and

platelet function.[2,14] As with many other NSAIDs, meloxicam and carprofen are highly absorbed in the stomach and small intestine mucosa, metabolized, and cleared in the bile, urine, and feces. Meloxicam excretion is primarily renal in mice,[1] whereas carprofen excretion is fecal.[30] COX-1 and COX-2 inhibitors damage the mucosa of the small intestine by reducing the mucosal prostaglandin E2 production, causing intestinal hypermotility, promoting nitric oxide synthesis, and increasing myeloperoxidase activity.[24]

Several reports discuss the ulcerogenic effect of high dose meloxicam. Mice develop gastrointestinal ulceration when given meloxicam at 17.5 to 35 mg/kg orally once a day for 3 mo.[13] This exceedingly prolonged dosing regimen may not be relevant for postoperative management yet based on these data we did not expect to see gastrointestinal ulceration in the current study. Toxicity has also been evaluated in C57BL/6N mice after SC injection of 20 mg/kg of meloxicam for 6 d.[22] While the principal adverse effect reported in that study was subcutaneous and dermal lesions associated with meloxicam at 5mg/mL, 1 of 4 mice developed gastritis.[22] We did not observe any skin lesions in our study when giving the 5 mg/mL concentration of meloxicam other than the bruising; however, we did not examine the skin for histologic lesions. Unlike the previous study,[22] our study found evidence of gastric ulceration in 4 of 18 of the meloxicam-treated mice (histologic score of 2 or greater), with 2 cases evident after the 3-d treatment and 2 cases evident after the 7-d treatment. Similar to the previous study,[22] we found mild gastritis without ulceration in the saline (2 of 18), carprofen (2 of 18), and meloxicam (4 of 18) treated mice. These findings likely represent background lesions of minimal significance; however, a possibility remains that if treatment was continued, the lesions would progress to gastric ulceration. While we used the higher concentration meloxicam (5 mg/mL), using a lower concentration of meloxicam would be unlikely to reduce the incidence of gastric lesions given that the overall dose of meloxicam would be identical.

The clinical significance of the histologic evidence of gastritis requires a more thorough assessment; however, in this study, we did not observe any evidence of overt adverse effects such as changes in behavior, posture, body condition, or facial grimacing. While a reduced body weight in the presence of gastritis is possible, body weight was not measured in this study. Although subclinical evidence of gastritis was associated with meloxicam treatment after 3 and 7 d of treatment, the lesions had resolved by 7 d after cessation of treatment. While gastritis may be subclinical in this study, the addition of other stressors, such as surgery, may result in more overt clinical signs. In addition, this study was conducted in female CD1 mice, and the results may vary in male mice or in other strains.

The fecal occult blood test was used to identify grossly undetectable blood in the feces. If identified, it may have originated from a gastric ulcer. Fecal occult blood was identified in 9 of 18 of the meloxicam-treated mice, compared with 2 of 18 of the carprofen-treated mice and 1 of 18 saline-treated mice. One saline-treated mouse had a positive fecal occult blood test from samples collected at necropsy. While care was taken in collecting the fecal pellets, blood contamination of the fecal pellet could have occurred during collection. This could explain positive tests in mice without histologic evidence of gastritis.

Serum chemistries were performed to evaluate organ toxicities, particularly liver and renal, associated with the high dose. No difference was detected in the liver parameters (ALP, ALT, AST, total bilirubin) or renal parameters (BUN and creatinine) in the meloxicam- or carprofen-treated mice as compared with the saline-treated mice, regardless of the duration of treatment. While we did not perform a complete blood count to evaluate for anemia, which could accompany gastric ulcers;[28], other chemical changes associated with gastric ulcers and hemorrhage were not present.[18,28] Mice treated with 3-d of meloxicam had a lower serum albumin concentration than did the carprofen and saline-treated groups. Hypoalbuminemia may occur with gastric bleeding in other species.[10,25,27] However, the level of albumin in this study was within published reference intervals of 2.5 to 4.8,[8,19] and is likely not clinically significant. Globulins were higher in the meloxicam treated group as well compared with the carprofen- and saline-treated groups. Changes in globulins associated with ulcerative gastritis would more likely result in a hypoglobulinemia rather than an increase,[10,28] and this finding is also not clinically significant. The lack of any clinically significant serum chemistry changes associated with the high doses of meloxicam and carprofen is similar to other studies.[22]

As the dosing regimens for treating pain in mice become more refined, specifically as doses are escalated, care should be taken to ensure that the toxic side effects do not impact the welfare of the mice. In this study, we evaluated the toxic effects of high doses of meloxicam and carprofen in female CD-1 mice. Our results indicate that mice given meloxicam at the high dose of 20 mg/kg daily for 3 to 7 d had a higher incidence of gastric ulceration, which was prevalent after 7 d of treatment. In contrast, mice did not develop gastric ulceration after a high carprofen dose of 20 mg/kg daily for 3 to 7 d. No serum chemistry changes suggested hepatic or renal toxicity. Based on these findings, high-dose meloxicam should be used cautiously, whereas high-dose carprofen does not appear to be associated with any toxicities. The efficacy of high-dose NSAIDS for the treatment of postoperative pain and the duration of treatment continue to need further investigation.

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