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Injection-site Reactions to Sustained-release Meloxicam in Sprague–Dawley Rats

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An extended-release formulation of the NSAID meloxicam (MSR) is used to provide 72 h of continuous analgesia in many species, including rodents. Although standard formulations of meloxicam are frequently used in rats with no observable injection-site reactions, the potential adverse effects from MSR have not been characterized sufficiently nor has a prospective study of these effects been performed in rats. To address this deficiency, we evaluated injection-site reactions after a single subcutaneous administration of MSR (n = 16) or sterile saline (SC, n = 6) in the flank of age- and sex-matched Sprague–Dawley rats. Mass and erythema scores were measured daily for 2 wk, and injection sites were collected for histopathology after euthanasia. Rats were randomly selected for euthanasia at 7 d (n = 12) or 14 d (n = 10) after injection to capture the subacute and chronic phases of mass and erythematic lesion formation. No rats in the SC group developed lesions, whereas all 16 MSR-treated rats developed masses. The median time to first mass in the MSR treatment group was 3 d (95% CI, 2–3 d), and nearly 8 d for erythema (95% CI, 6.7–9.1 d). The trajectory of mass lesion severity showed rapid progression from score 1 at onset (day 2 or 3) to score 2 for almost all animals by day 5 or 6. Histopathology was characterized by localized inflammation with central necrosis and peripheral fibrosis, with some sections showing developing draining tracts. Given the high prevalence and severity of localized skin reactions, MSR analgesia should be considered carefully for Sprague–Dawley rats.

Abbreviation: MSR, sustained-release meloxicam

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Pain management is a critical component for the care and welfare of animals used in research. Determining the appropriate analgesic drug is essential for optimizing pain management while avoiding unwanted side effects. Drug selection is important not only to maximize animal wellbeing but also to minimize confounding effects on study outcomes. NSAID are commonly used analgesics for animals in research and clinical settings. NSAID are not controlled substances and thus offer greater accessibility and ease of use than other analgesics, such as opioids, and are easier to manage in research settings. In addition, NSAID tend to be well-tolerated and highly effective.[3,4,10,16,21]

Meloxicam is a commonly used NSAID analgesic with a high therapeutic index and high tissue tolerability.[3,10,21] A single injection of meloxicam is suggested to provide analgesic coverage for 12 to 24 h in rodents.[6] Analgesic regimens often extend past a 12- to 24-h range, thus requiring repeated dosing. Recurrent handling and fluctuations in plasma levels associated with multiple doses can result in stress and pain in recovering animals.[1] To combat those issues, sustained-release SR formulations of analgesics, both opioids and NSAID, have become available in the past few years. One pharmaceutical company released a sustained-release formulation of meloxicam (MSR), which proposes 72 h of analgesic coverage from a single injection. Sustained-release formulations, when effective, are optimal for maintaining effective plasma levels of analgesics while reducing animal handling stress and personnel labor.[1,14,15,17]

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Numerous studies have been conducted to assess the pharmacokinetic profile and efficacy of MSR in several species.[2,8,9,12,14,15,19,20] Although efficacy throughout the full 72-h window has been demonstrated to various degrees, adverse reactions have not specifically been assessed, particularly for longer durations of assessment.[2,8,9,12,14,15,19,20] In addition, the manufacturer of MSR does not specify the compound formulation but indicates that it was intended for human use, and it has not specifically been proven safe in other animals.[22] Injection site lesions of varying severity have been noted tangentially in MSR studies involving parrots[11] and cynomolgus macaques[2] but thus far have not been identified in rodents. However, sustained-release formulation of the opioid buprenorphine has been noted to cause erythematous skin lesions in several species,[7] including mice[5] and rats.[11] Studies evaluating MSR efficacy in rodents typically extended to 72 h only, which may be insufficient time for the development of adverse granulomatous skin reactions to occur.[14,19] Skin site reactions with the progression of lesions beyond the typical 72 h drug efficacy-testing window have the possibility of being overlooked and unreported. In addition, small lesions that may be present within the 72-h efficacy window can easily be missed by cage-side observations if animals are not palpated daily.

Understanding the prevalence, severity, and prognosis for adverse drug reactions is essential in making informed decisions regarding the use of those drugs. Adverse reactions may have a particularly negative effect when they interfere with or confound research aims and therefore, should be avoided when possible. After we anecdotally observed lesions after injections of MSR in 2 female Sprague–Dawley rats that had been used for embryo transfer procedures, we hypothesized that Sprague–Dawley rats are susceptible to injection site reactions after a single injection of MSR. In this study, our objective was

to determine the rate of emergence of localized tissue reactions after a single subcutaneous injection of MSR in rats. In addition, we sought to characterize, both grossly and histologically, any skin lesions that developed within acute (7 d after injection) and chronic (14 d after injection) phases of progression.

Materials and Methods

Animals. This study was approved by IACUC of the University of California–Davis, and rats were maintained in accordance with the standards established by the *Guide for the Care and Use of Laboratory Animals*.[13] Sprague–Dawley rats (11 male and 11 female; age, 16 wk) were singly housed in IVC (Lab Products, Seaford, DE) on a 12:12-h (lights on, 1800) light:dark cycle at 68 to 79 °F (20.0 to 25.6 °C) and 30% to 70% humidity on corncob bedding. All rats were fed standard chow (no. 2918 18% protein rodent diet, Envigo Teklad Diets, Madison, WI) and received sterile water (Hydropac, Lab Products, Seaford, DE) ad libitum.

Animals were housed in an SPF vivarium and were free of the following pathogens: all ectoparasites and endoparasites, sialodacryoadenitis virus, Sendai virus, pneumonia virus of mice, hantavirus, rat parvovirus, Kilham rat virus, H1 virus, reovirus 3, lymphocytic choriomeningitis virus, murine encephalomyelitis virus, rat theilovirus, cilia-associated respiratory bacillus, *Mycoplasma arthritidis*, and *Mycoplasma pulmonis.*

Administration of MSR and scoring of lesions. Age and sex-matched Sprague–Dawley rats were randomly assigned to 1 of 2 treatment groups: MSR (n = 16; 8 male and 8 female; age, 16 wk) or sterile saline control (SC, n = 6, 3 male and 3 female). The number of animals was based on consultation with a statistician and determined to be sufficient to provide sufficient power in light of preliminary observations of 2 animals exhibiting visible lesions. In alignment with the principals of the 3Rs, animal numbers were minimized in this study. Each rat received a single subcutaneous injection of MSR (4 mg/kg; ZooPharm, Wildlife Pharmaceuticals Windsor, CO) or an equivalent volume of sterile saline (0.9% Sodium Chloride Injection, Hospira Worldwide, Irvine CA). Injections were administered over the sacral region by using a sterile 1-mL syringe with a 25-gauge, 5/8-in. needle (Becton Dickenson, Franklin Lakes, NJ); in our experience, this location is typically used for clinical purposes. The average injection volume was 0.38 mL, with a range of 0.38 to 0.79 mL. A highly experienced technician performed all injections under the supervision of a veterinarian. The vials of sterile saline and MSR used in the study were submitted to the University of California–Davis Clinical Pathology Laboratory to confirm sterility after use. Rats were examined daily for overall health and were palpated for lesions at or near the injection site for 7 or 14 d after injection by a single treatment-blinded observer. All palpated masses were examined carefully and assigned mass and erythema scores that characterized the presentation and severity of the lesion (Figure 1).

Necropsy and histologic assessment. Rats were randomly selected and submitted to the Comparative Pathology Laboratory for necropsy and histologic assessment at 7 d (6 male [4 MSR, 2 SC] and 6 female [4 MSR, 2 SC], n = 12) or 14 d (5 male [4 MSR, 1 SC] and 5 female [4 MSR, 1 SC], n = 10) of the study. On arrival, animals were euthanized via carbon dioxide asphyxiation and cervical dislocation and underwent gross examination and collection of the tissue surrounding the injection site for histopathologic assessment. Injection site reactions—characterized by firm, brown to orange, ellipsoid nodules in the subcutis at the site of administration—were measured (length, width, height of ellipsoid in cm), and sampled. Measurements were converted to size by calculating the area of an ellipsoid ($4 / 3\pi$ [length × width × height]).

Injection site tissues (skin and subcutaneous injection site) were submersion-fixed in 10% neutral-buffered formalin for 72 h. Formalin-fixed tissues were processed routinely, embedded in paraffin, sectioned at 4 to 5 µm, and stained with hematoxylin and eosin. Histopathology was read by a single board-certified veterinary anatomic pathologist (DI), who was blinded to treatment group. Injection sites were evaluated for presence (score, 1) or absence (score, 0) of inflammation; when inflammation was present, the character of the inflammatory response was recorded.

Statistical analysis. Statistical analysis was performed by using SAS statistical software (version 9.4, SAS Institute, Cary, NC). The proportion of rats in each group that developed lesions at any point during the follow-up was calculated and compared by using the Fisher exact test and a P value of less than 0.001 to identify significance. A life-table approach was used to characterize time to first reported mass or erythema lesion, generate a Kaplan–Meier plot, and estimate median time to first lesion and 95% CI; saline and MSR treatments were compared by using a log-rank test.

The mass and erythema of lesions were characterized daily on an ordinal scale from 0 (no lesions) to 4. A subset of 8 MSR rats were euthanized on day 7; all other rats were followed for the full 14 d. The proportion of rats in each group that developed masses or erythemic lesions at any point during the follow-up was calculated and compared by using the Fisher exact test. A life-table approach was used to characterize time to first reported mass lesion, generate a Kaplan–Meier plot, and estimate median time to first lesion and 95% CI); saline and MSR treatments were compared by using a log-rank test.

A more detailed examination of the MSR treatment group modeled the individual rat's lesion trajectories on an ordinal scale from 0 to 4. A generalized linear model was used to analyze the data, allowing for repeated observations of the rats. A logistic link function was used to capture the S-shaped curve for mass lesions from 0 to 2 (because only one rat scored greater than 2 on a single occasion, observations were truncated at 2), with a binomial error structure. We considered both a linear function of time (on the logistic scale) and a quadratic function of time, to allow for a possible late flattening of the trajectories.

The postmortem size of the injection site reaction and binary lesion scores (presence or absence of injection site inflammation) were analyzed by unpaired t testing and nonparametric Mann–Whitney testing, respectively. Prism 7.0 (GraphPad Software, La Jolla, CA) was used for all histopathologic statistical analyses (significance defined as $P \leq 0.05$).

Results

Mass and erythema scores. Regardless of sex or dose volume, all (100%, n = 16) of rats in the MSR treatment group developed mass lesions after injection. None of the rats in the SC group developed masses, whereas all 16 rats in the MSR treatment group developed lesions ($P < 0.001$, Fisher exact test). Neither mass nor erythema prevalence differed between males compared with female rats.

The median time to first mass lesion in the MSR treatment group was 3 d (95% CI, 2 to 3 d), showed a very consistent pattern, and again was highly significantly different from the control group ($P < 0.001$, log-rank test). Detailed examination of the trajectories of mass lesion severity in the MSR-treated group showed rapid progression from stage 1 at onset at day 2 to 3 to stage 2 for almost all animals by day 5 or 6. A simple linear

Score	Erythema	Mass
0	No visible reaction	No palpable thickening or mass
1	Mild alopecia or erythema	Palpable thickening, borders undefined, cannot measure
2	Moderate alopecia or erythema; overlying skin intact	Palpable mass, borders defined, measurable, overlying skin intact
3	Moderate alopecia or erythema, with partial thickness ulceration	Palpable mass, borders defined, measurable, with partial thickness ulceration
4	Moderate to severe alopecia or erythema, with full-thickness ulceration	Palpable mass, borders defined, measurable, with full-thickness ulceration

Figure 1. Scales used for scoring the erythema and mass of injection-site reactions.

model on the logistic scale fit well, with a trend for quadratic term driven primarily by a single animal that reverted to stage 1 at the last time point. Observed mean scores followed the fitted curve well. The trajectories are well summarized by stating that the average across animals of the ratio of score: 2 – score (1.98 initially) increases 7.24-fold (95% CI, 2.07- to 25-fold; $P = 0.003$) every day. On this scale, the median time to reach stage 1 (first visible lesion) is 2.5 d, consistent with the life-table estimate of median onset by 3 d.

None of the rats in the SC group developed any erythemic lesions, whereas 4 of the 16 rats in the MSR treatment group developed erythema lesions ($P < 0.54$, Fisher exact test.). The MSR treatment group was not significantly different from the control group ($P = 0.23$, log-rank test). The mean time to first erythema lesion in the MSR group was 7.9 d (95% CI, 6.7 to 9.1 d), showing a very consistent pattern. Of the 4 rats to develop erythemic lesions, 3 were scored at level 3 with severe lesions, and 2 had draining tracts. The remaining rat received a score of 1 and maintained level 1 erythema until euthanasia at day 7.

Gross and histopathologic findings at 7 and 14 d. At 7 d after injection, adverse reactions associated with a single dose of MSR were associated with ulceration (draining tracts) in 2 of the 8 rats (25%, Figure 2 A); no ulceration was present in the remaining 6 rats (Figure 2 B). All 8 rats exhibited ellipsoid discrete to multifocal and coalescing tan to orange-red subcutaneous nodules (Figure 2 C). The mean area of the subcutaneous nodules was 3.7 ± 3.5 cm^2.

At 14 d after MSR injection, subcutaneous nodules remained present, but were less prominent and lighter in color. No ulceration was observed. All 8 rats exhibited ellipsoid discrete to multifocal and coalescing tan to orange subcutaneous nodules (Figure 2 D). The mean area of the subcutaneous nodules was 2.6 ± 1.5 cm^2.

Histologically, at 7 d after MSR injection, the subcutaneous nodules appeared as foci of necrotizing panniculitis with intralesional amphophilic material (interpreted as the MSR formulation) and extensive peripheral fibroplasia (Figure 3 A and B). At 14 d after MSR injection, the inflammatory response showed less necrosis and more foamy macrophages, interpreted as granulomatous to xanthomatous panniculitis (Figure 3 C and D). The shift in the inflammatory response toward a more macrophage-rich pattern was considered to indicate that the lesions were resolving. At 14 d after MSR injection, peripheral fibrosis was more organized than previously.

At 7 d after injection, a trend ($P = 0.066$) toward larger nodules was detected in the MSC groups as compared with the SC group, which had no detectable nodules (Figure 4). The size of the subcutaneous nodules at 14 d was significantly ($P = 0.041$) greater in the MSR group than in the SC group. MSR-treated groups (at both 7 and 14 d after injection) were significantly ($P = 0.002$ and $P = 0.0022$, respectively) more likely to exhibit

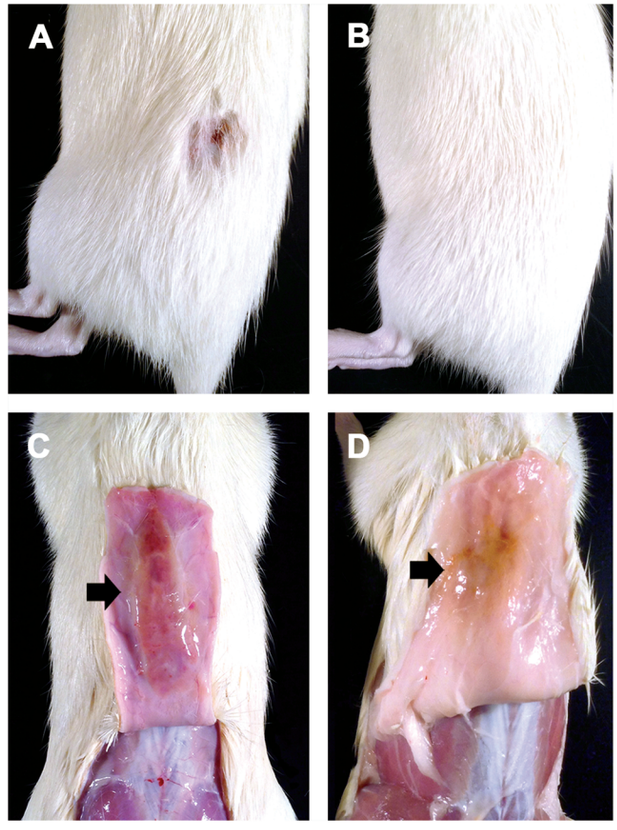

Figure 2. At 7 d after injection of 12-wk-old male and female Sprague–Dawley rats, adverse reactions associated with a single dose of sustained-release meloxicam (MSR) were variable, from (A) overt to (B) not evident on external examination. (C) At 7 d after MSR injection, adverse reactions formed single to multiple coalescing, tan to orange-red, oblong subcutaneous nodules. (D) At 14 d after MSR injection, adverse reactions were still identifiable as subcutaneous nodules.

subcutaneous injection site reactions than the SC rats. The histologic findings in MSR-treated rats were consistent with injection-related panniculitis. At the 14-d time point, the injection site reaction was undergoing various stages of resolution, with the granulomatous to xanthomatous reactions being more advanced.

Discussion

Our results demonstrate that Sprague–Dawley rats developed injection-site reactions after a single dose of MSR. Failure of the saline injection to produce any reaction suggests that these lesions are not due to poor injection technique. The frequency and severity of these lesions merit careful consideration or

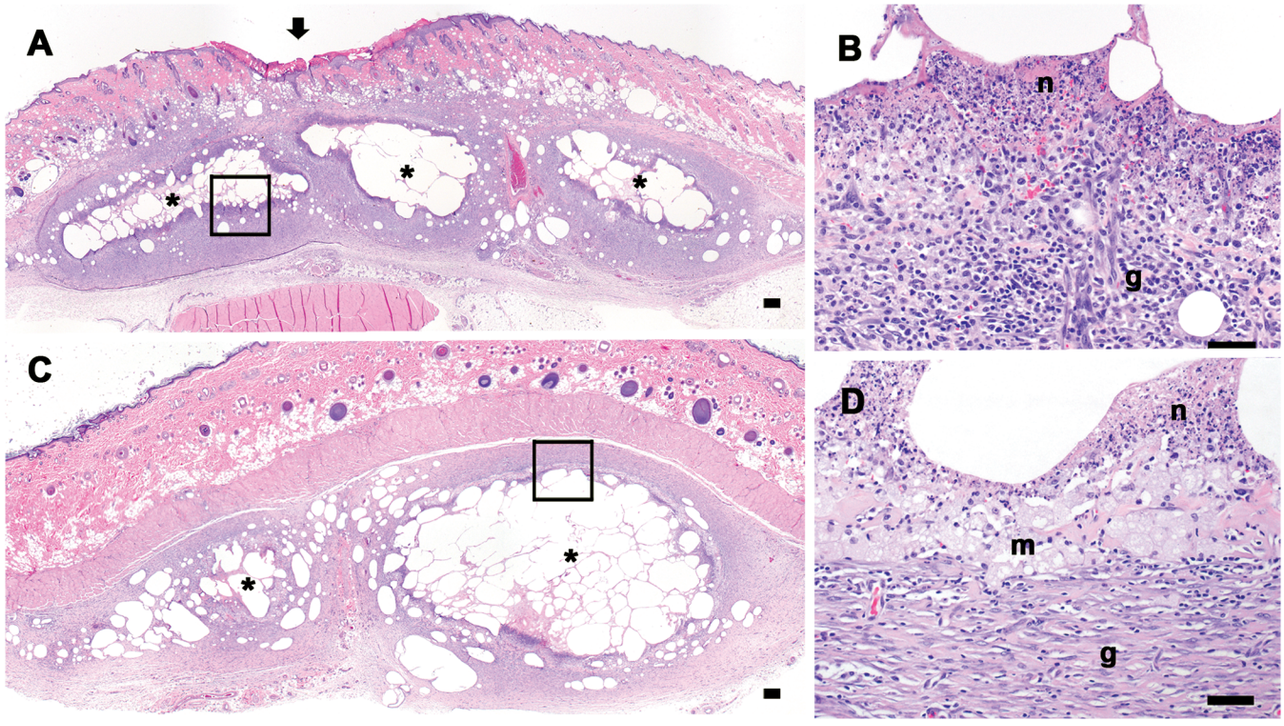

Figure 3. Histologically, adverse injection site reactions to a single dose of MSR are characterized by chronic necrotizing panniculitis. (A) At 7 d after MSR injection, the overlying epidermis can be ulcerated (arrow). Areas of central necrosis (asterisks) are surrounded by intense inflammation. Hematoxylin and eosin staining; magnification, 20×; bar, 50 µm. (B) Higher magnification of boxed area in panel A, demonstrating necrotic inflammatory debris (n) and immature granulation tissue (g). Hematoxylin and eosin staining; magnification, 200× magnification; bar, 500 µm. (C) At 14 d after MSR injection, central areas of necrosis (asterisks) are surrounded by decreased inflammation and more organized granulation tissue. Hematoxylin and eosin staining; magnification, 20×; bar, 50 µm. (D) Higher magnification of boxed area in panel B, demonstrating a predominance of foamy macrophages (m) and more organized granulation tissue (g). Hematoxylin and eosin staining; magnification, 200×; bar, 500 µm. All images are oriented with the superficial aspect of the skin at the top and the underlying subcutaneous tissue at the bottom.

avoidance of MSR when selecting an analgesic regimen because these lesions may adversely affect animal welfare and study outcomes. Rats with injection site lesions resulting in open wounds with draining tracts may require premature euthanasia, thus negatively affecting study outcomes. In addition, inflammation caused by MSR injections may introduce confounding factors in studies assessing inflammation as a variable. Conversely, the presentation of the lesions noted between the acute (7 d after injection) and chronic (14 d after injection) groups suggests that lesions may resolve spontaneously, given sufficient time. MSR may be an inappropriate analgesic for studies in which inflammation and lesion development would be confounding factors.

MSR is widely available for use in rodents in research and clinical settings, yet adverse skin reactions have been reported infrequently, and those reports have involved nonrodent species.[2,12] Given that 100% of the rats that received MSR in the current study developed lesions, we were surprised that the reported incidence of adverse reactions in rodents is so low. We suspect that a major reason underlying this low reported incidence is that lesions were missed or underreported due to the prolonged time between injection and the initial emergence of a lesion. The median presentation times were 2 to 3 d for palpable masses, 5 to 6 d for the mass to develop clearly defined borders, and more than 7 d for erythema to develop; consequently, lesions may not have been present or discernible during a 72-h efficacy or pharmacokinetic study window. Other studies in rodents reported skin lesions after an injection of sustained-release buprenorphine, which is produced by the same compounder as MSR; in those reports, lesion development followed a similar time course to the first lesion as we saw here for MSR.[5,11] Although the compounded formulation may not contain the same sustained-release component, our study indicates that lesions may develop beyond the 72-h window of analgesic efficacy.

Another explanation for low reporting was that many of the lesions we identified were not visually apparent and were identified only by thorough palpation and careful assessment of skin under the haired areas. Masses remained fully furred and absent of erythema, particularly in the first 3 d, making them almost exclusively discernable through palpation. The more subtle lesions identified in our study were confirmed through histologic assessment but were easy to miss through gross observations. Daily handling including palpation of the injection site was not expressly performed in other studies and is not typically done in laboratory animal settings, because it may be impractical and would eliminate the benefit of sustained-release drugs to reduce handling. Finally, lesions could also be inaccurately attributed to other etiologies, including fight wounds, barbering, or dermatitis if observed grossly.

Our study was successful in clearly identifying that MSR causes localized skin reactions, but additional studies are warranted to further classify the trajectory of the lesions' formation and resolution. Future studies could benefit from including an examination of animals treated with the standard formulation of meloxicam to provide a more direct comparison of the standard with the sustained released-formulation. Although one study[18] has reported lesions in as many as 25% of rats after multiple meloxicam injections, the 100% incidence of lesions

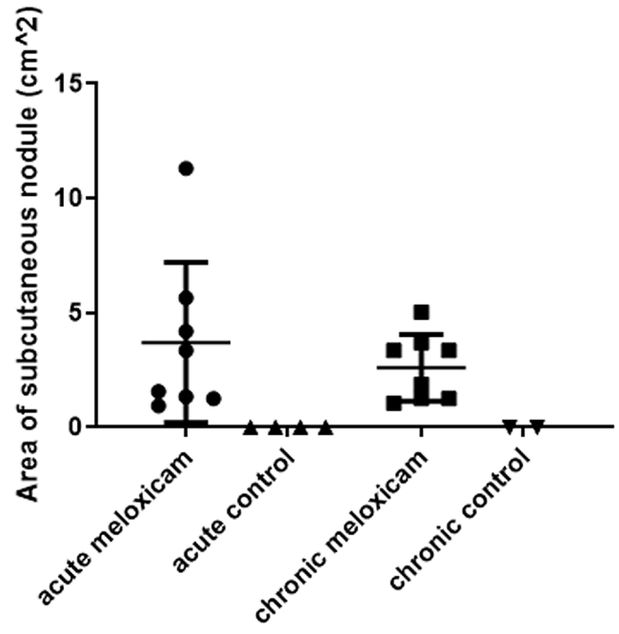

Figure 4. Postmortem area measurements of subcutaneous nodules (cm^2) in MSR and SC groups. Acute MSR and SC groups were euthanized at 7 d after injection (6 male rats [4 MSR, 2 SC] and 6 females [4 MSR, 2 SC], n = 12); chronic MSR and SC groups were euthanized at 14 d after injection (5 males [4 MSR, 1 SC] and 5 females [4 MSR, 1 SC], n = 10).

after a single injection of MSR in our study indicates that the sustained-release formulation is more problematic. We did not administer standard-release meloxicam as a control in this study; we instead opted for sterile saline. The SC group allowed us to rule out injection technique and the tissue damage and irritation that may occur from any injection, regardless of how mild the substance. We did not see data consistent with pressure necrosis in either treatment group, and dose volumes were well below the recommended maximal volume. Although we don't suspect that the injection location was a factor, examination of sacral compared with interscapular injections would confirm that reactions are independent of location site. Having larger treatment groups in future studies also would allow us to statistically probe the trajectory of erythematous lesions, which we were unable to assess given the low number of animals in the current study. Lastly, observing animals beyond 14 d would allow us to further quantify the tendency of mass lesions to resolve over time, as indicated in our comparison of 7-d and 14-d histology.

Because all MSR-treated rats developed lesions in the present study, we recommend caution when prescribing and administering this formulation in Sprague–Dawley rats. In addition, we suggest establishing the safety of MSR in other strains of rats before using it in research studies, particularly in cases where inflammatory responses may confound study outcomes. The presentation and prevalence of adverse effects are variable among species and strains; therefore, we recommend palpation of injection sites in addition to careful observation of animals that receive MSR. For research studies in which MSR-induced lesions may be a confounding factor, MSR tolerance could be assessed on a subset of animals before administering it to study subjects. Although a sustained-released analgesic may offer several benefits, the possibilities of lesion formation, compromised animal welfare, and potential confounding study factors should be evaluated when planning a study.

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