Postmortem Study of Meloxicam Toxicity in One Month Old Puppy

Chalise, S. and Singh, D. K.
Nepal Polytechnic Institute, Bharatpur, Chitwan
Corresponding email: sushil.chalise.sc@gmail.com

Abstract

An intramuscular administration (2.5 mg per kg) of meloxicam caused anorexia, vomiting, and diarrhea within a few hours, followed by unconsciousness, anemia, severe dehydration, and death within 12 hours in a one-month-old puppy. Postmortem findings showed hepatomegaly and acute hemorrhagic inflammation of the abomasum, colon and kidneys. Histological examination revealed tubular hemorrhage and tissue necrosis, with widespread vascular damage in the kidneys. This study emphasized cautious dosing and monitoring of meloxicam in young puppies.

Key words: Meloxicam, puppy, NSAID

Introduction

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) which is most widely used in veterinary practices for the treatment of fever, inflammation, osteoarthritis and other long term or short-term painful conditions (Yocum et al., 2000; Fleischmann et al., 2002). Meloxicam decreases pain and inflammation by reducing the production of prostaglandin (Engelhardt, 1996) through the selective inhibition of the enzyme COX-2 (Türck et al., 1996).

Unintentional intoxication of meloxicam frequently occurs in small animals due to accidental ingestion of medications not designated for them and dispensing errors such as mismatch between a prescription and the medication (Kannan et al., 2019). This report highlights the fatal toxicity of intramuscular administration of meloxicam in puppy.

Case History

A young one-month old local breed puppy was admitted at NPI Veterinary Teaching Hospital with a history of anorexia, vomiting on the previous day, and loss of consciousness following next day after the administration of 0.5 ml (equivalent to 2.5 mg) of meloxicam intramuscularly at one of the private vet shops in Bharatpur. The puppy showed symptoms of disorientation, lethargy,

congested eyes, diarrhea and anemia. The vitals recorded at arrival included temperature (98.6°F), CRT (4 sec) and heart rate (70 beats per minute).

Gross Findings

Postmortem investigation revealed notable swelling and high congestion in the liver and anterior part of gastric mucosa. Linear hemorrhage was clearly spotted on the colon. There was presence of feces in the large intestine. Minute striations was observed in the cortex of kidney. Urinary bladder was full of urine. The tissue samples of kidneys, liver and intestine were fixed in 10% neutral buffered formalin for preparation of histopathological slide.

Figure.1 Postmortem examination of puppy

Figure.2 Congestion in liver and anterior part of stomach

Figure.3 Spotted linear hemorrhage in colon

Figure.4 Minute striation in cortex of kidney

Histopathological findings

1. Kidney (Acute renal tubular necrosis):

Histopathological examination revealed to acute renal tubular necrosis characterized by degenerative and necrotic alterations at the tips of the renal papillae (Fig 7), marked widespread

Figure.5 Serosanguinous fluid in small intestine

Figure.6 Accumulation of urine in urinary bladder

hemorrhage in renal tubules (Fig 8) and glomeruli (Fig 9), homogenous proteinous eosinophelic material accumulated in some of the tubules (Fig 10), and in interstitial space. The renal tubular hemorrhages were severe degeneration, necrosis, shrinkage (atrophy) and desquamation of renal epithelial cells (Fig 11). However, the basement membrane remained intact.

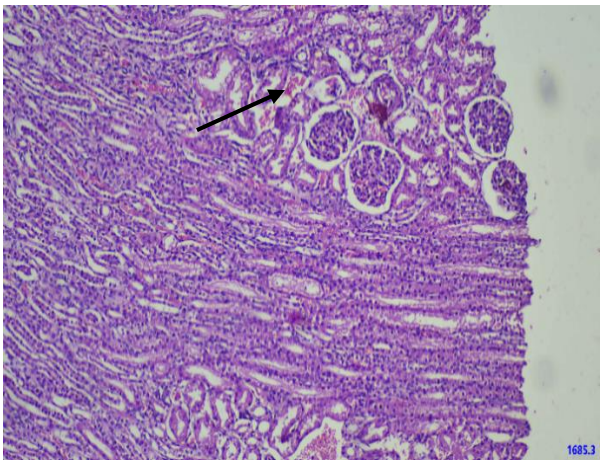

Figure.7 Widespread hemorrhage on renal tubules (single head arrow) shown under 10X microscope.

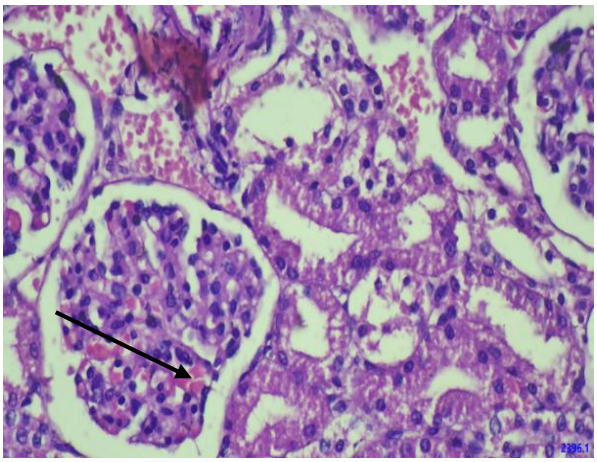

Figure.8 Hemorrhage on glomerulus viewed under 40X microscope (single head arrows).

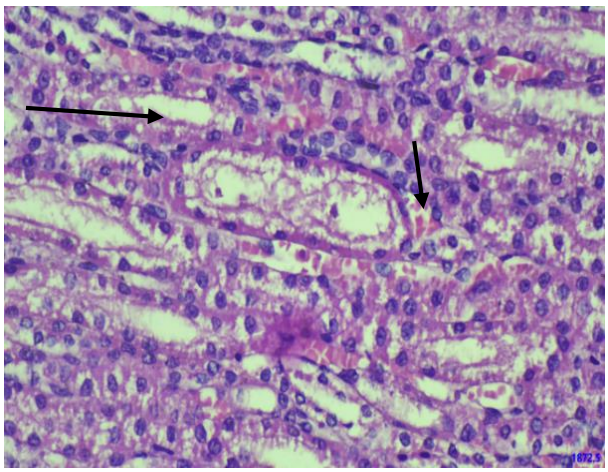

Figure.9 Acute tubular necrosis (straight arrow) and hemorrhage in renal tubule (downward arrow) viewed under 40X microscope.

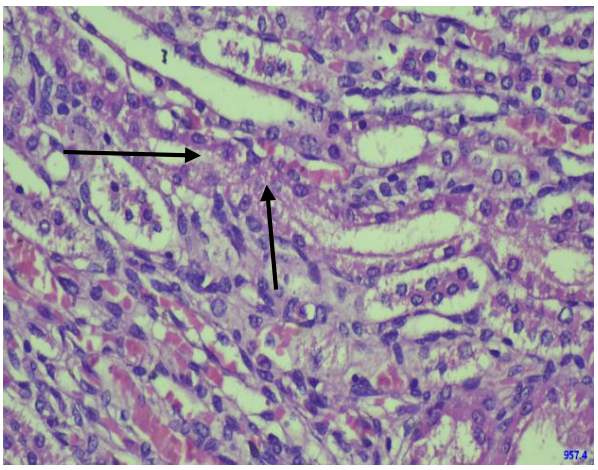

Figure.10 Accumulation of homogenous proteinous eosinophelic materials in tubules (straight arrow) and interstitial space (upward arrow) viewed under 40X microscope.

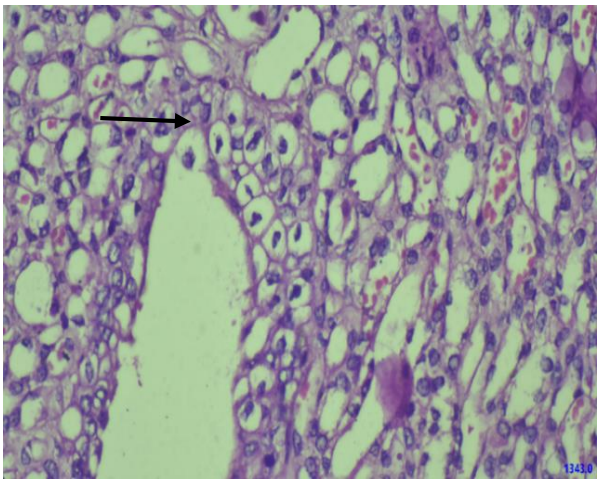

Figure.11 Degeneration and necrosis at the tip of papillae (single head arrow) viewed at 40X microscope.

2. Liver

The histopathological lesion in the liver included the dilation of centrilobular sinusoid, severe congestion and edema surrounding the central vein (Fig 12 and Fig. 13).

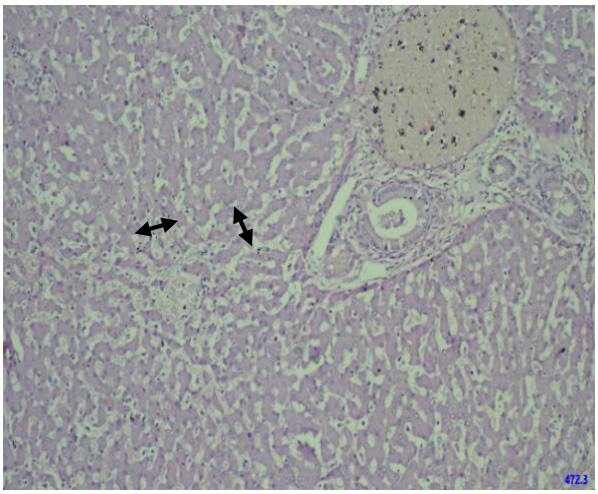

Figure.12 Centrilobular sinusoid dilation (double head arrows) viewed under 10X microscope

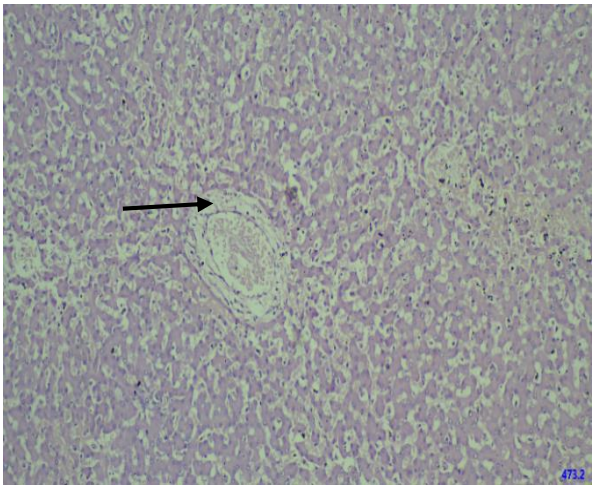

Figure.13 Edema and severe congestion around central vein (single head arrow) viewed under 10X microscope

3. Intestine

Histopathological investigation revealed necro-hemorrhagic enteritis, characterized by inflamed and damaged intestinal epithelial tissue, accompanied by the infiltration of inflammatory cells (Fig. 14 and Fig. 15).

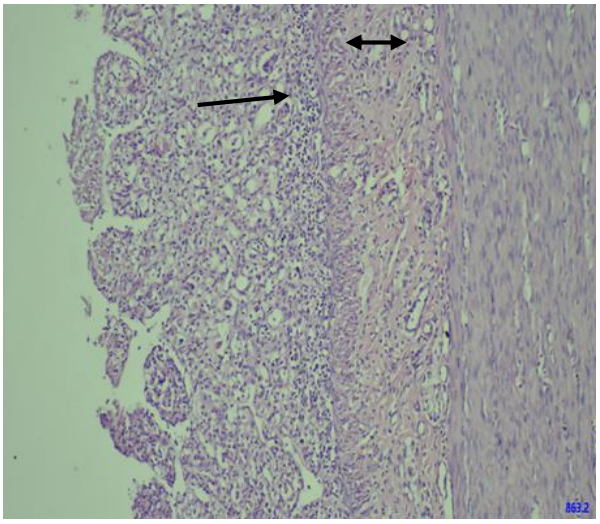

Figure.14 Hemorrhage in epithelium (single head arrow) and infiltration on intestinal epithelial cell (double head arrow) viewed under 10X microscope

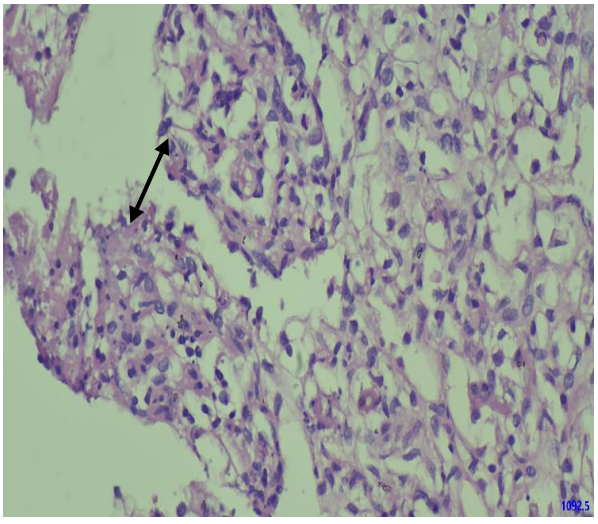

Figure.15 Necro-hemorrhagic enteritis (double head arrow) viewed under 40X microscope

Discussion

The presented case of meloxicam toxicity in a young puppy highlights the severe consequences of inappropriate administration of non-steroidal anti-inflammatory drugs (NSAIDs) in small animals. Meloxicam is a commonly used NSAID for pain management in veterinary medicine, primarily in dogs, but its administration should always be approached with caution, especially in neonates and young animals due to their limited metabolic capacity and physiological immaturity (Horster and Valtin, 1971). The preferred dosing regimen for meloxicam involves an initial administration of 0.2 mg/kg body weight intravenously (IV) or subcutaneously, followed by a maintenance dose of 0.1 mg/kg/day administered orally (PO) (Gruet et. al., 2013). The case was brought to the hospital after administration of 2.5 mg meloxicam intramuscularly, which is 12.5 times higher than the therapeutic dose. Drug bioavailability, volume of distribution, and total systemic clearance remain constant up to 5 times the recommended dose for use in dogs (Metacam, 2009).

The clinical presentation, specifically anorexia, vomiting, loss of consciousness, disorientation, lethargy, congested eyes, diarrhea, and anemia were consistent with the study of Kannan et al., 2019 in a six-year-old Labrador dog with a dispense dose 20 times higher standard dose. In this case, the puppy's young age, small size, and relatively large dose of drug exacerbated the toxic effects, leading to death.

The postmortem findings including significant pathological changes across renal, intestinal and hepatic remained consistent with previous studies (Mahaprabhu et. al., 2011). The gastrointestinal distress manifested as congested anterior stomach and linear colon hemorrhage, emphasized the widespread vascular effects of meloxicam. Gastrointestinal distress occurred due to irritation in the lining of the gastrointestinal mucosae, leading to increased blood flow and causing damage to the blood vessels in the colon, resulting in hemorrhage (Longley et. al., 2022).

The histopathological findings in the kidney suggest a complex pattern of injury and degeneration in the tubules. The presence of renal tubular hemorrhage, severe epithelial cell degeneration, and tissue necrosis indicate significant damage to the renal tubules. Hemorrhage in the renal tubules decreases prostaglandin vasodilators as a result of the inhibition mechanism of meloxicam and increases vasoconstriction, resulting in rupture of blood vessels (Weir, 2002). The disparity in basement membrane status between the current study, where it remained undamaged, and Mohammad's research, which documented basement membrane loosening in male mice after 10

days of continuous 0.4 mg meloxicam administration, could be attributed to the acute toxicosis nature of this study, potentially explaining the contrast in outcomes (Mohammed et al., 2019). The observed degeneration, desquamation, and atrophy of tubular cells indicated ongoing cellular damage and dysfunction. Tubular damage may be due to ischemia as a result of inhibition of prostaglandin production in small arterioles (Andalib et al., 2011). Vascular degenerative changes in the renal tubules further contributed to the compromised kidney function (Hssoni and Salman, 2019). Additionally, the marked hemorrhage in the glomerulus and necrotic alterations at the renal papillae tips signify extensive kidney damage (Sellers et al., 2005). The accumulation of homogenous proteinaceous material in tubules and interstitial spaces suggested potential issues with protein handling and filtration (Sellers et al., 2005; Bumethiak et. al., 2017). These findings collectively indicated severe kidney pathology and impairment of renal function in the present case.

The histopathological examination of the liver revealed significant pathological changes. The dilation around the centrilobular sinusoids suggested impaired hepatic circulation leading to hydropic degeneration of centrilobular hepatocytes corroborates with the finding of earlier study (Ahmad et al., 2017). The pronounced presence of edema and severe congestion surrounding the central vein underlined the severity of vascular and parenchymal damage caused by meloxicam toxicity (Hssoni and Salman, 2019).

The histological findings in the intestine of the puppy, characterized by hemorrhage within the epithelial tissue, infiltration of inflammatory cells into the intestinal epithelium, and the presence of necro-hemorrhagic enteritis, can be attributed to the toxic effects of a meloxicam overdose. An overdose can disrupt the delicate balance of prostaglandins in the body, leading to severe inflammation, damage to blood vessels, and eventual necrosis in the intestinal lining (Enberg et. al., 2006; Burukoglu et. al., 2016).

Conclusion

This case study highlighted the consequences of a meloxicam toxicity in a young puppy. The puppy's age, small size, and excessive dose resulted in rapid damage to health, characterized by a range of clinical symptoms and severe pathological changes in various organs. Meloxicam toxicity led to compromised hepatic, renal, and gastrointestinal functions. These findings showed the

importance of cautious dosing and monitoring when using NSAIDs like meloxicam in veterinary medicine, especially in neonates and young animals. Timely recognition and intervention are crucial to preventing such deadly outcomes in small animal patients.

References

Ahmad, A., Nizamani, Z. A., and Qasim, M. (2017). Histopathological effect of Meloxicam (Preferential COX-2 inhibitor NSAID) on liver and kidney of rabbit. International Journal of Biosciences (IJB), 11(3), 148–158. https://doi.org/10.12692/ijb/11.3.148-158

Andalib, S., Naeini, A. M., Garjani, A., Asl, N. A. and Abdollahi, A. (2011). A comparative study pertaining to deleterious effects of diclofenac sodium and meloxicam on kidney tissue in rats. EXCLI Journal, 10, 149–154.

Bumethiak, N., El-Drieny, E., El-Drussi, E., and El-Agory, M. (2017). Effect of Meloxicam on Hematological and Kidney Histopathoogical Changes in Male Mice. British Journal of Medicine and Medical Research, 21(4), 1–8. https://doi.org/10.9734/bjmmr/2017/32315

Burukoglu, D., Baycu, C., Taplamacioglu, F., Sahin, E., and Bektur, E. (2016). Effects of nonsteroidal anti-inflammatory meloxicam on stomach, kidney, and liver of rats. Toxicology and Industrial Health, 32(6), 980–986. https://doi.org/10.1177/0748233714538484

Enberg, T. B., Braun, L. D., and Kuzma, A. B. (2006). Gastrointestinal perforation in five dogs associated with the administration of meloxicam. Journal of Veterinary Emergency and Critical Care, 16(1), 34–43. https://doi.org/10.1111/j.1476-4431.2005.00157.

Engelhardt, G. (1996). Pharmacology of meloxicam, a new non-steroidal anti-inflammatory drug with an improved safety profile through preferential inhibition of COX-2. British Journal of Rheumatology, 35(SUPPL. 1), 4–12. https://doi.org/10.1093/rheumatology/35.suppl_1.4

Fleischmann, R., Iqbal, I., and Slobodin, G. (2002). Meloxicam. Expert Opinion on Pharmacotherapy, 3(10), 1501–1512. https://doi.org/10.1517/14656566.3.10.1501

Gruet, P., Seewald, W., and King, J. N. (2013). Robenacoxib versus meloxicam for the management of pain and inflammation associated with soft tissue surgery in dogs: A randomized, non-inferiority clinical trial. BMC Veterinary Research, 9. https://doi.org/10.1186/1746-6148-9-92

Horster, M., and Valtin, H. (1971). Postnatal Development of Renal Function: Micropuncture and Clearance Studies in the Dog. The Journal of Clinical Investigation, 50(4), 779–795. https://doi.org/10.1172/JCI106549

Hssoni, Z. A., and Salman, R. J. (2019). Morphological and histological study by induced of piroxicam on the kidney, liver, and stomach in the rats. Drug Invention Today, 11, 2642–2647.

Kannan, K., Saravanan, M., Ram Kumar, P. K., Arul Kumar, T., Senthil Kumar, S.,and Premalatha, N. (2019). Meloxicam toxicity in Labrador dog due to dispensing error and its reversal by misoprostol. Indian Veterinary Journal, 96(10), 78–80.

Longley, M. J., Baines, S. J., and Chanoit, G. (2022). Colonic perforation in 4 dogs following treatment with meloxicam. Journal of Veterinary Emergency and Critical Care, 32(3), 413–419. https://doi.org/10.1111/vec.13170

Mahaprabhu, R., Bhandarkar, A. G., Jangir, B. L., Rahangadale, S. P., and Kurkure, N. V. (2011). Ameliorative effect of Ocimum Sanctum on meloxicam induced toxicity in wistar rats.

Toxicology International, 18(2), 130–136. https://doi.org/10.4103/0971-6580.84265

Metacam. (2009). 3144.

Mohammed, N. M. H., El-Drieny, E., El-Drussi, I. S., Al-Agory, M., and Gheth, E. M. M. (2019). Histopathological changes in liver tissue induced by meloxicam in male mice. Researchgate.Net, 10(1), 6059–6063

Sellers, R. S., Senese, P. B., and Khan, K. N. M. (2005). Interspecies differences in the nephrotoxic response to cyclooxygenase inhibition. Drug and Chemical Toxicology, 27(2), 111–122. https://doi.org/10.1081/DCT-120030726

Türck, D., Roth, W., and Busch, U. (1996). A review of the clinical pharmacokinetics of meloxicam. British Journal of Rheumatology, 35(SUPPL. 1), 13–16. https://doi.org/10.1093/rheumatology/35.suppl_1.13

Weir, M. R. (2002). Renal effects of nonselective NSAIDs and coxibs. Cleveland Clinic Journal of Medicine, 69 Suppl 1(SUPPL. 1). https://doi.org/10.3949/CCJM.69.SUPPL_1.SI53

Yocum, D., Fleischmann, R., Dalgin, P., Caldwell, J., Hall, D., and Roszko, P. (2000). Safety and efficacy of meloxicam in the treatment of osteoarthritis: A 12-week, double-blind, multiple-dose, placebo-controlled trial. Archives of Internal Medicine, 160(19), 2947–2954. https://doi.org/10.1001/archinte.160.19.2947