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Reversal of Hepato-renal Impairment Induced by Meloxicam Paracetamol Toxicity in a Labrador Dog

M. Saravanan[1*], N. Premalatha[2], P. K. Ramkumar[1], K. Kannan[1], R. Apoorva[2], M. Venkatesan[2], K. Jayalshmi[2], S. Yogeshpriya[2] and S. Senthilkumar[2]

[1]Veterinary Clinical Complex, Veterinary College and Research Institute, TANUVAS, Orathanadu, Thanjavur – 614 625, Tamil Nadu, India; sara82vet@yahoo.com
[2]Department of Veterinary Medicine, Veterinary College and Research Institute, TANUVAS, Orathanadu, Thanjavur – 614 625, Tamil Nadu, India

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Abstract

An 8 years old male Labrador dog was referred to Small animal Medicine Referral Clinic, Veterinary Clinical complex, Veterinary College and Research Institute, Orathanadu for fever, anorexia, hematemesis and melenic stools. The dog on treatment with 2 ml of Meloxicam Paracetamol combination IM, along with Injection Oxytetracycline and fluid therapy for 3 days by locally and did not respond to treatment thus was referred. Clinical dullness, lethargy, respiratory distress, visible mucosal jaundice, ecchymosis on ventral abdomen was noticed. Physical examination revealed, halitosis, ulceration in the tip of the tongue, dehydration, pre scapular LN enlargement, distended abdomen, fluid thrill and splenomegaly. Hematology revealed anemia and thrombocytopenia. Biochemical analysis revealed Hyperbilirubinemia, Elevated BUN, Creatinine, AST, ALT, ALP and hypoalbuminemia. Abdominal ultrasound reveled splenomegaly, focal hyperechoic liver parenchyma, cortex echogenicity of right kidney and perirenal fluid accumulation. ECG revealed peaked T wave. Radiography revealed hepatosplenomegaly. Hemato-biochemical alteration was monitored before and after therapy. Animal was managed with fluid therapy, Acetylcysteine, Amino acid and supportives and the dog had an uneventful recovery.

Keywords: Dog, Hepatotoxicity, Hyperbilirubinemia, Meloxicam, Paracetamol

1. Introduction

Non steroidal anti-inflammatory drugs are widely used in the Veterinary practice especially to manage soft tissue and orthopedic pain[1]. NSAIDs exert their effect by inhibiting cyclooxygenase enzymes. In food animal practice combination of NSAIDs with Paracetamol preparation are widely used for anti inflammatory and anti pyretic effect, because combinations of Paracetamol and NSAIDs provide additive effect[2]. Meloxicam is one among NSAIDs used in the Veterinary practice and causes GI ulcer and renal insufficiency, if administered continuously and over dose[3]. Treatment with Paracetmol injections is not followed in pet practice, but in some cases over the counter administration or dispensing errors of Paracetamol cause hepatotoxicity[4]. Administration of Meloxicam and Paracetamol combination causes severe ill effect rather than administration of single injection in pet animals. Here such a case has been reported in a Labrador dog due to administration of Inj. Meloxicam Paracetamol combination resulted sever hepatic and renal insufficiency and it was successfully managed along with uneven full recovery.

*Author for correspondence

2. Material and Methods

2.1 Case History

An 8 years old male Labrador dog was referred for fever, anorexia, emesis and voiding of black tarry colored feces. The dog on treatment for fever with 2 ml of Inj. Meloxicam Paracetamol combination IM, along with Injection Oxytetracycline and fluid therapy for 3 days by locally and did not respond to treatment thus was referred to VCC, VCRI ,Orathanadu. On clinical examination the dog was dull, lethargic, exhibited discomfort in lying down and getting up, dyspnoea, mild elevation of body temperature 39.5^{0}C, conjunctival mucosa (Figure 1), penile mucosa jaundiced (Figure 2) along with echymosis of ventral abdomen. Physical examination revealed dehydration, pre scapular LN enlargement, halitosis, ulceration in the tip of the tongue (Figure 3), distended abdomen, fluid thrill, splenomegaly (Figure 4), hematemesis (Figure 5) and black tarry colored feces and hematuria (Figure 6).



Figure 1. Dog - Yellow tint (Iatric) conjunctiva.



Figure 4. Dog - Abdominal distention.



Figure 2. Dog - Iatric penile mucosa.

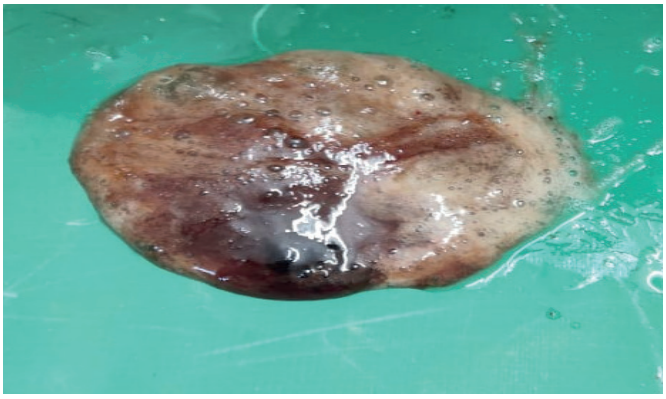


Figure 5. Dog – Hematemesis.

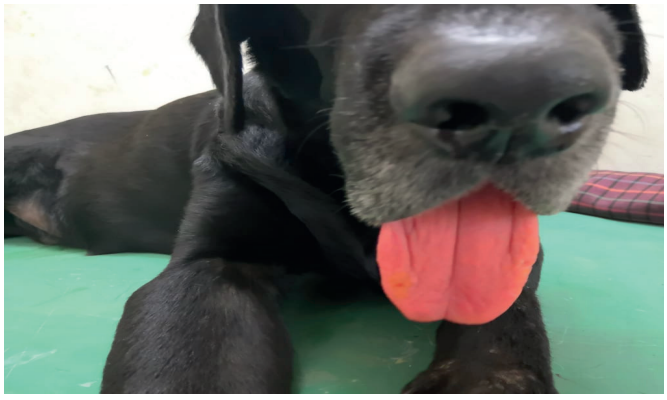


Figure 3. Dog - Tongue ulceration.



Figure 6. Urine – Hematuria.

Sample collected: Fecal sample was collected to rule out helminthes, PBS for haemoparasites, EDTA blood sample was collected before and after treatment for hematology and biochemistry evaluation to assess the treatment. Automated hematology analyzer (VETSCAN HM5, Germany) was used for the hematology. Automated biochemical analyzer (SELECTRA PRO XS) was used for biochemical estimation. Urinalysis was done by quantification Urinalyzer.

Special diagnostic procedures like Abdominal Ultrasound (ESAOTE MYLAB ONE™ with convex 3.5-10 MHz transducers), Radiography (Siemens), ECG (Genx3, BPL India) and Doppler BP were performed as per the standard operating procedure.

Treatment initiated with Intravenous injections of Ringers lactate, Inj. 5% dextrose, as fluid replacers, Inj. Haemaccel @ 10ml/kg IV as plasma volume expander, Inj. Acetylcysteine loading dose is @ 140 mg/kg followed by @70 mg/kg IV as to cyto and hepatoprotective, Inj. Astymin- 3 @ 10 ml IV daily as essential amino acids for nutritional support to reduce catabolism in stress conditions. Inj. Ondencetron @ 0.1 mg/kg IV and Inj. Pantoprazole @ 1 mg/Kg IV as anti emitis and to reduce gastric ulcer and Inj. Vitamin B complex @ 1 ml IV as supportive. Oral medication were initiated after remission vomiting administrated with Oral Syrup Hemup, Syrup Gluton liv, Syrup Sorbilin and Tab. Ursodeoxycholic acid @ 10 mg/kg BID PO to improve hematopoietic, reduce hepatobiliary disorder and supportive. The continuous treatment protocol for a period of 8 days from the day of presentation and followed by two periodical review once in 14 days were recorded. Treatment protocol was initiated with symptoms, laboratory results and maintained based on their clinical recovery.

3. Results

Hematology revealed anemia and thrombocytopenia. Peripheral blood smear revealed absence of blood parasites. Urinalysis revealed the presence of haematuria (+), Bilirubinuria (++), Urobilinogen (+) Ketonuria (+) and Proteinuria (++). Biochemistry examination revealed elevation of BUN, Creatinine, Total and Direct Bilirubin, decrease in total protein and albumin. Hematology (Table 1) and biochemistry (Table 2) alteration were monitored for the therapeutic efficacy and the same are tabulated.

There was a gradual reduction of Hb, PCV, RBCs and platelet count up to four days of treatment and from 5th day post treatment there was improvement in the hematological values.

Elevated values of serum creatinine returned to normalcy following 3rd day post treatment and BUN returned to normalcy after 5th day post treatment. Elevated Bilirubin levels reduced 7th day post treatment only. Fluctuation of total protein level became normal on day 7 (PT). Reduced level of albumin was maintained and slight improvement was observed from day 8 (PT) and regained normalcy on day 14. Elevation of liver enzymes viz. ALT, AST and ALP level were observed and gradually subsided from day 14 (PT) onwards. Lowered serum Glucose normalized during subsequent days of initiation of treatment. Other biochemical parameters like Cholesterol, potassium and chloride levels were within their normal reference levels.

Abdominal ultrasound examination revealed focal hyper echogenicity of liver parenchyma, Splenomegaly, anechoic fluid between liver-spleen and liver-right kidney, Hyper echogenicity on cortex, size of 8.31 x 4.24 cm (right kidney) and 7.95 x 3.56 cm (left kidney) was visualized (Figures 7-11). The ultrasound study on day 14 revealed reduction in size of spleen, absence of fluid, followed by normal ultrasound structures on day 28 (PT).

Radiographic examination revealed Hepato-splenomegaly and normal thoracic study.

Electrocardiogram on the day of presentation reveled ST segment elevation and it become normal post treatment (Figures 12 and 13). Systolic BP of 100 mm Hg was noticed on day of presentation which was recorded by hand held Doppler BP monitor.

Clinical improvement was appreciated from third day onwards like activity, improvement of nature of stools, gradual improvement of jaundice, regression of emesis and improved food habits. After a week the animal was very active and alert, normal appearance, normal food intake followed by normal urination and defecation.

4. Discussion

According to the Animal Poison Control Center (APCC) data, ibuprofen, aspirin, naproxen, deracoxib, meloxicam, diclofenac, piroxicam, indomethacin, nabumetone and etodolac were the commonly recorded NSAIDs toxicities[5] wherein dog is the most cost commonly affected species.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) are the most widely used in Veterinary practice[6]. Meloxicam is the one among the NSAIDs used as analgesic, anti-inflammatory and antipyretic by cyclooxygenase type 2 (COX-2) inhibitor[7], The recommended dose of Meloxicam in dog is initially @ 0.2 mg/kg bwt followed by 0.1 mg/kg/day[5,7]. Meloxicam is 97% protein bound nature and has a low volume of distribution (0.32 L/kg) and a prolonged elimination half-life around 12–36 h.[8].

Table 1. Evaluation of hematological alterations due to Meloxicam Paracetamol toxicity in a Labrador dog

Parameters	Reference	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14	Day 28
WBC (10^3/µl)	6-17	7.5	5.59	5.72	6.89	9.54	17.85	14.44	5.17	8.35	9.85
LYM (%)	12-30	20.8	15.8	18.6	21.6	35.7	33.4	55	56	46.1	38.9
MON (%)	2-4	3	9.8	5.8	4.4	0.6	4.1	0.6	6.9	1.9	8.2
NEU (%)	62-87	74.7	72.8	73.8	72.9	62.5	62	42.8	33.7	49.1	51
EOS (%)	0-8	1.4	1.5	1.8	1	1.1	0.3	1.2	3.3	2.1	1.6
BAS (%)		0.1	0	0	0	0.1	0.1	0.4	0.1	0.9	0.3
RBC (10^6/µl)	5.5-8.5	5.08	4.36	3.52	3.7	2.55	3.58	3.72	5.9	3.93	4.41
HGB (g/dl)	12-18	10.1	8.7	7	5.7	4.8	7.2	7.5	8.5	7.8	9.2
HCT (%)	37-55	26.44	22.43	18.27	19.16	13.07	18.65	19.12	31.19	20.37	22.95
MCV (fl)	60-77	52	51	52	52	51	52	51	53	52	52
MCH (pg)	19.5-24.5	20	19.9	19.9	15.3	18.9	20.1	20.2	14.5	20	20.9
MCHC (g/dl)	31-34	38.3	38.7	38.5	29.6	36.8	38.6	39.4	27.4	38.5	40.1
RDWs (fl)		34.4	33.6	32.8	33.6	32.8	33.6	35.9	35.9	36.7	37.5
RDWc (%)		17.1	17.1	16.3	16.6	16.6	16.6	18.2	16.8	18.1	18.4
PLT (10^3/µl)	200-500	47	27	12	38	57	199	289	26	357	171
PCT (%)		0.05	0.03	0.01	0.04	0.06	0.21	0.29	0.03	0.35	0.14
MPV (fl)	3.9-11.1	10.3	10.7	9.8	10	9.9	10.3	9.9	10.4	9.7	7.9
PDWs (fl)		16.3	14.9	11.5	14.9	14	14.3	11.8	16.3	12.3	8.1
PDWc (%)		39.4	36.5	33.1	37.4	37.7	37.9	34.4	39.4	36.1	30.5

Table 2. Evaluation of serum biochemical alterations due to Meloxicam Paracetamol toxicity in a Labrador dog

Parameters	Reference	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 14	Day 28
BUN (mg/dl)	6-25	296	232	99	53	28	24	30	23	37	41
Creatinine (mg/dl)	0.5 - 1.6	2.6	1.38	0.66	0.55	0.54	0.49	0.5	0.43	0.85	0.77
D. Bilirubin (mg/dl)	0 - 0.4	2.98	4.16	3.02	1.42	0.82	0.31	0.45	0.49	0.35	0.26
ID. Bilirubin (mg/dl)		2.37	3.58	2.1	1	0.7	0.91	0.46	0.38	0.29	0.21
T. Bilirubin (mg/dl)	0.1-0.3	5.35	7.74	5.12	2.42	1.52	1.22	0.91	0.87	0.64	0.47
Glucose (mg/dl)	70-138	61	90	91	89	89	65	81	69	85	87
Cholesterol (mg/dl)	125 - 300	122	107	110	136	150	181	192	200	156	165
Total protein (g/dl)	5.0 - 7.4	7.1	6.1	5.9	6.2	6.3	7.3	7.5	7.5	7.7	7.9
Albumin (g/dl)	2.7- 4.4	1.41	1.42	1.55	1.63	1.87	2.03	2.15	2.14	2.3	2.86
Globulin (g/dl)	1.6-3.6	5.69	4.68	4.35	4.57	4.43	5.27	5.35	5.36	5.4	5.04
ALT (U/L)		185	180	213	242	291	286	216	186	152	76
AST (U/L)	15-66	126	179	167	156	141	59	35	27	32	26
ALP (U/L)	3 - 60	179	395	365	300	20	21	35	20	47	365

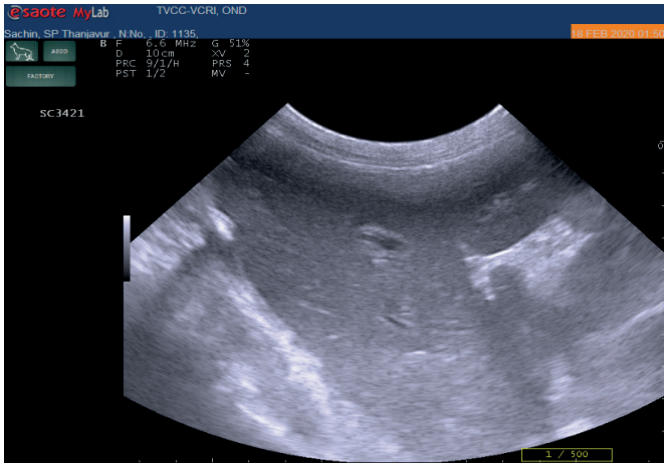


Figure 7. USG - Dog - Focal hyperechogenic liver parenchyma.

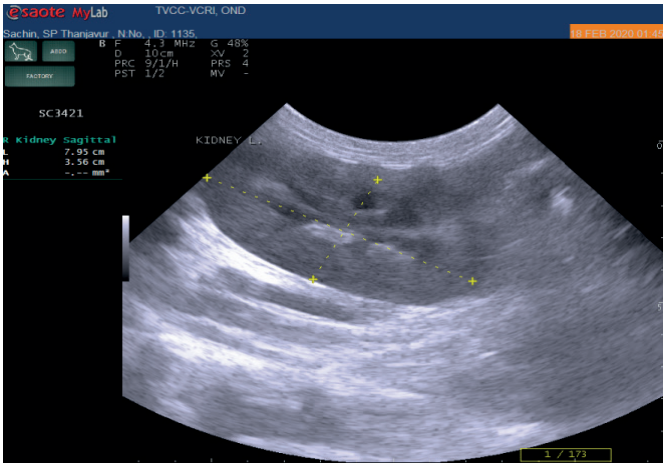


Figure 9. USG - Dog - Kidney - Left hyperechogenic medullar area.

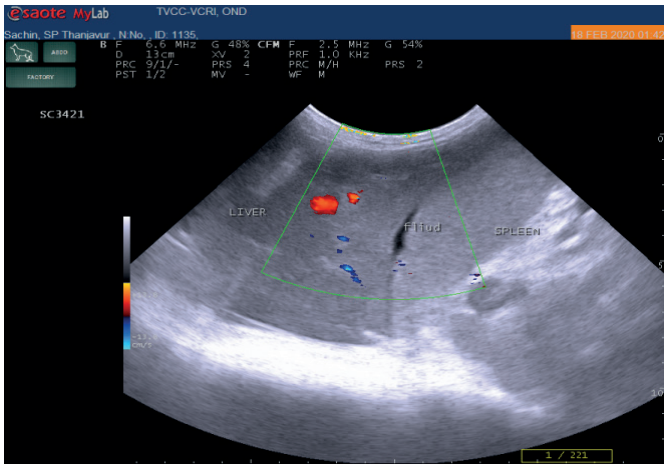


Figure 8. USG - Dog - Fluid between liver and spleen.

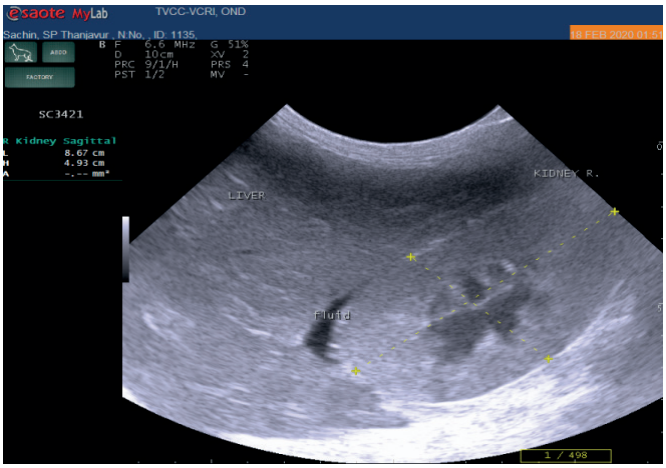


Figure 10. USG - Dog - Fluid between liver and right Kidney.

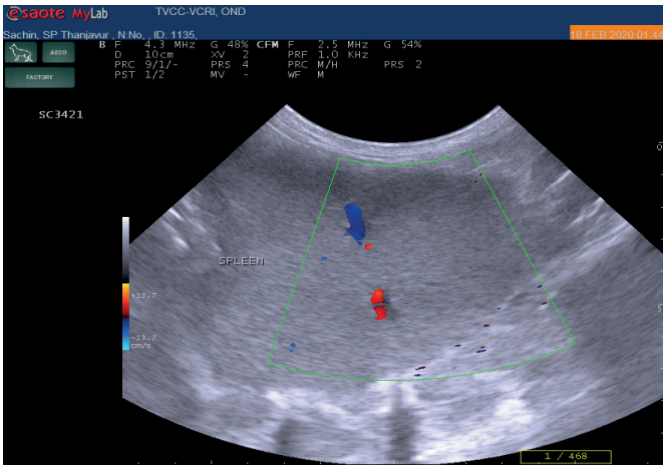


Figure 11. USG - Dog - Splenomegaly

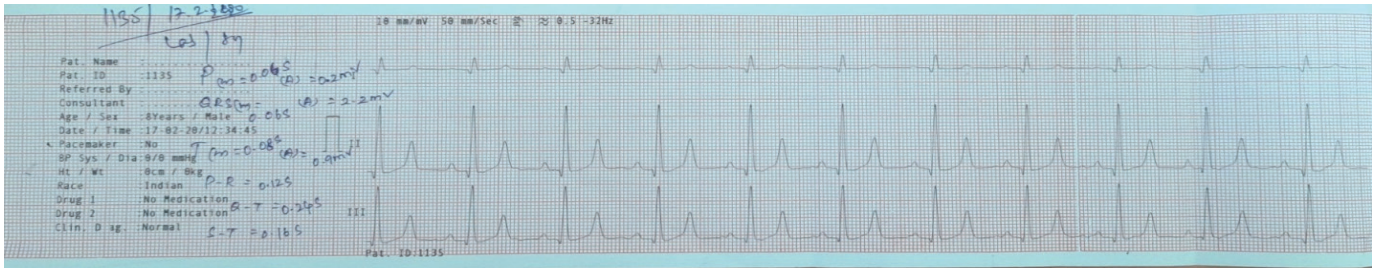


Figure 12. ECG - Dog - Peaked T wave (before treatment).



Figure 13. ECG - Dog - Normal ECG (After treatment).

Another important NSAIDs toxicity in pets is due to Paracetamol or acetaminophen. Paracetamol toxicity is mainly because of the over-the-counter (OTC) medications, either by deliberate administration of medicament by the pet owners or by accidental consumption of improperly stored drug where Paracetamol is the common household medications[4]. The recommended dose of Paracetamol in dog is @10-15 mg/kg wt (Mathews, 2002). Paracetamol toxicity causes hepatic failure, renal insufficiency and hematologic disorders[9] as distinctly evidenced in the present study.
Paracetamol induced hepato toxicity attributed to the metabolite of N-acetyl-p-benzoquinone imine (NAPQI), which decreases the capacity of glucuronidation and covalent bonding with many intracellular proteins, thus increasing liver enzymes[10,11].

NSAIDs exhibit their effect by inhibition of cyclooxygenase pathways to block prostaglandins (PGE2 and PGI2) secretions, this PG is essential for maintenance of renal blood flow and glomerular filtration rate[3,5]. During the NSAID of Meloxicam toxicity the production of PG is impaired, which results in ischemic renal injury followed by acute renal failure, if appropriate therapeutic measures not taken. NSAIDs induced renal impairment is usually temporary and it can be reverse by withdrawal of drug and intravenous fluid therapy[5].
Hernandez-Avalos et al.[12] reported that Paracetamol was as effective as Meloxicam and carprofen for post-surgical analgesia in bitches subjected to elective ovariohysterectomy. Paracetamol has similar analgesic and antipyretic properties to NSAIDs, hence the combination with NSAIDs like Meloxicam induce more toxicity, because of their synergistic action[13/]

The effect of combinations of Paracetamol /NSAIDs is superior to that of either component alone and even lower doses can have adverse effects[14]. But in the present case combination of Meloxicam/Paracetamol were administered high dose for continuously days, more over the administered drug combination are indicated in large animals only not for pet practice. This is the reason for the ailment of the animal.
The common clinical signs of Meloxicam toxicity are dullness, depression, congested mucosa and black tarry feces[3]. Anorexia, weakness, tachypnoea, dyspnoea, cyanosis, icterus, hypothermia, lethargy and vomiting were observed in dogs due to Paracetamol toxicity[4]. The clinical signs were correlated with the present case.

NSAID toxicity can also result in hepatic failure along with renal damage, such animals monitoring of liver-specific enzymes like ALT, AST, ALP and GGT were very much supportive for the therapeutic protocols.

Anemia and thrombocytopenia may be attributed to the toxic effect of Paracetamol metabolites on hemoglobin[15]. Elevated bilirubin level is clearly supported by yellowish discolorations (Jaundice) of all the visible mucous membrane.

The increased echogenicity of the liver parenchyma reflected the hepatic damage and it could be supported by the eleva-

tion of bilirubin (direct and indirect), AST, ALT and ALP followed by reduction of albumin. Ascites in the present case may be by the acute inflammation of the liver parenchyma due to Paracetamol toxicity. Ultrasound evidence of Splenomegaly confirmation could be due to the increased destruction of RBCs and compensatory mechanism on the anemic crisis of the body system. Hyper echogenicity of renal cortex of right kidney is suggestive of renal involvement and it is supported by the elevation of Creatinine. Radiography also confirmed the enlargement of liver and spleen. Similar findings were reported in Meloxicam toxicity by Kannan et al.[3] and in Paracetamol toxicity by Salem et al.[5].

Elevated S-T segment and prolonged P-R interval in early stage may be due to electrolyte and conduction disturbance led by the hemodynamic disturbance during the toxicity, but no clear mechanism were found.

General treatment protocol for NSAID toxicity in dogs are to support and symptomatically treat including aggressive decontamination of the toxic drug, Intravenous fluid therapy, GI protectant, antiemetics and prostaglandin analogs and recent addition of IV lipid emulsions are the treatment options[16–17].

N-acetylcysteine is well-recognized antidote for acetaminophen-induced toxicity and its anti-inflammatory action promote hepatic microcirculation and improves tissue oxygen delivery[18].

Ursodeoxycholic acid stimulates bile flow which increases the elimination of endogenous toxins excreted in the bile, especially bilirubin and it has anti-apoptotic effects, stabilization of mitochondrial function and immunomodulatory actions[19].

Mathews[1] suggested that NSAIDs induced renal impairment is usually temporary and it can be reversed against withdrawal of drug and intravenous fluid therapy.

Rosenthal and Labato[20] reported that 50% of fresh-frozen type-matched canine plasma, followed by 6% hydroxyethyl starch was used to treat nonsteroidal anti-inflammatory drug overdose in dogs. Hypoalbuminemia is the common complication of liver failure, because albumin is synthesized in liver and it serves as plasma volume expanders to maintain oncontic pressure. Hence, in this case for temporary restoration of the oncotic pressure by commercially available plasma volume expanders was used.

Amino acid supplementation is essential in anorectic animals to support protein synthesis and spare tissue proteins from being catabolized through gluconeogenesis for speedy recovery from the illness[21].

5. Conclusion

Based on that authors were concluded that multimodal analgesic regimens were followed in veterinary practice to alleviate the pain, this multimodal analgesic regimens is like double edged weapon because combination of NSAIDs provide good analgesic effect but it can cause potent side effect like GI ulcer, hepatic and renal impairment followed by multi-organ failure, if not followed protocol. Hence judicial and proper dosage of drugs may prevent such incidences.

6. Acknowledgement

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