PATHOLOGY OF MELOXICAM TOXICITY IN COCKEREL BIRDS

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ABSTRACT

An experiment was conducted to study meloxicam toxicity in poultry. Toxicity was induced by oral administration of meloxicam to groups B, C and D @ 0.2, 0.4 and 0.8 mg/kg body weight respectively and group A served as a control. Haematological and biochemical parameters were studied at 0, 8, 24, 48 and 72 hrs of experiment. The observations revealed decrease in Hb, PCV, TEC along with leucocytosis and absolute heterophillia in groups C and D. Serum uric acid, creatinine, AST and ALT values were found elevated in groups C and D. The serum biochemical deviations in the present study indicated nephrotoxic and hepatotoxic effects of meloxicam in poultry at higher doses of the drug.

KEY WORDS : Cockerels, meloxicam, toxicity, Haematobiochemical

INTRODUCTION

There is a growing concern over the problem of vulture mortality caused due to use of non-steroidal anti-inflammatory drug diclofenac in veterinary practice to overcome acute and chronic inflammatory conditions. A ban on the use of certain NSAIDs has been imposed by some countries. Thus it has become imperative to explore other resources available to counteract the inflammatory conditions.

Amongst NSAIDs, meloxicam is hailed as one of the effective NSAID in veterinary practice. Meloxicam is COX-2 (Cyclo-oxygenase) specific inhibitor at its lowest therapeutic dose and is anti-inflammatory by inhibiting prostanoid synthesis in inflammatory cells (Mohapatra *et al*., 1993).

Keeping in view the popular use of meloxicam as NSAID and paucity of literature regarding its deleterious effects, the present study was under taken to evaluate its pathological impact on poultry and to correlate with reported vulture mortality due to NSAID diclofenac.

MATERIALS AND METHODS

Apparently healthy, day old 24 cockerel chicks obtained from Phoenix Hatchery, Jabalpur were reared under standard management conditions. All the birds were vaccinated against Ranikhet disease using Lasota strain on the 6th day and infectious bursal disease using intermediate strain on the 15th day of age. Birds were divided into 4 groups of 6 birds each. Meloxicam was administered at different doses of 0.2, 0.4 and 0.8 mg/kg body weight to groups B, C and D respectively as a single oral dose, whereas, group A birds were kept as control. All the birds were kept under observation for a period of 96 hrs after dosing for clinical signs of toxicity. Six birds from each group were sacrificed at 96 hrs of experiment to study gross and histopathological changes in liver, kidney and brain.

Necropsy and histopathology – A detailed post mortem examination of all the sacrificed birds was carried out and different organs were examined for the presence of gross lesions. Pieces of liver, kidney and brain were collected and fixed in 10 % formal saline solution. Tissues were routinely processed, 4-5 µm thick sections were cut and stained with haemtoxyline and eosin (HE) stains (Luna, 1968).

Haemato-biochemical studies – For haemato-biochemical studies blood samples were collected prior to the administration of meloxicam (0 hr), and subsequently at 8, 24, 48 and 72 hrs after

meloxicam administration. Serum was separated and used for the estimation of uric cid, creatinine, aspartate transaminase (AST) and alanine transaminase (ALT). Data collected during the experiment were subjected to analysis of variance to study the effect of period and treatment on haemato-biochemical parameters as per Snedecor and Cochran (1994).

RESULTS AND DISCUSSION

Clinical signs – The birds receiving varying levels of meloxicam did not exhibit any abnormal symptoms. No death due to meloxicam toxicity was recorded in any of the experimental groups.

Gross pathology – At 0.2 mg no significant gross lesions were seen. At 0.4 and 0.8 mg dose, liver showed few necrotic foci and congestion, kidneys were congested and mottled and brain revealed edema.

Histopathology – At 0.4 mg dose liver revealed congestion, perivascular necrosis (Photo 1). Hepatic toxicity due to other NSAIDs like nimesulide, diclofenac, paracetamol has been earlier reported by various authors (Aydin *et al.,* 2003; Bhaumik *et al*., 1995; Hedau *et al*., 2008; Mohapatra *et al*., 1993).

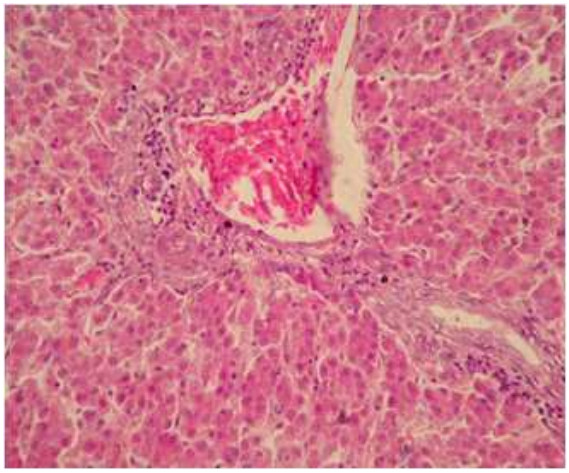

Photo 1 - Section of liver showing degenerative Changes and periportal necrosis. HE x 200

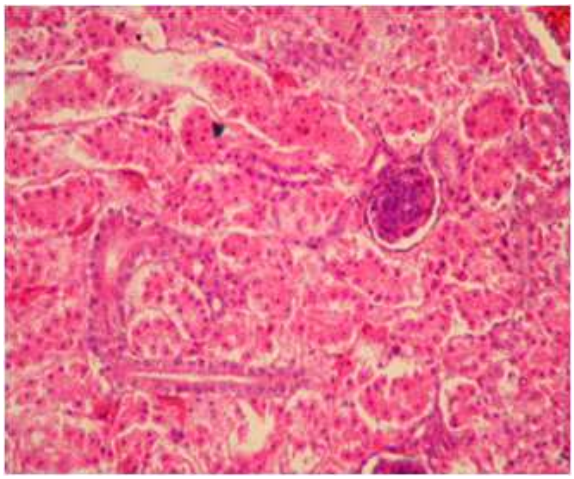

Photo 2- Section of kidney showing glomerular sclerosis and tubular degenerative changes. HE x 200.

Kidney revealed congestion in the birds of B and C group however, section of kidneys in group D revealed severe granular degenerative changes leading to occlusion of lumen along with sclerotic glomerular nephropathies (Photo 2). Nephrotoxic effect of NSAIDs has been previously reported (Alencar *et al.*, 2002; Aydin *et al.*, 2003; Gupta *et al*., 2000; Mohapatra *et al*., 1994). At 0.4 and 0.8 mg dose brain revealed degenerative changes, necrosis in perivascular spaces and glial cells around the site of injury (Photo 3).

Haematological studies – Results of haematological estimations are predicted in Table 1 and 2.

Birds receiving higher dose levels of meloxicam (0.4 and 0.8 mg) in groups

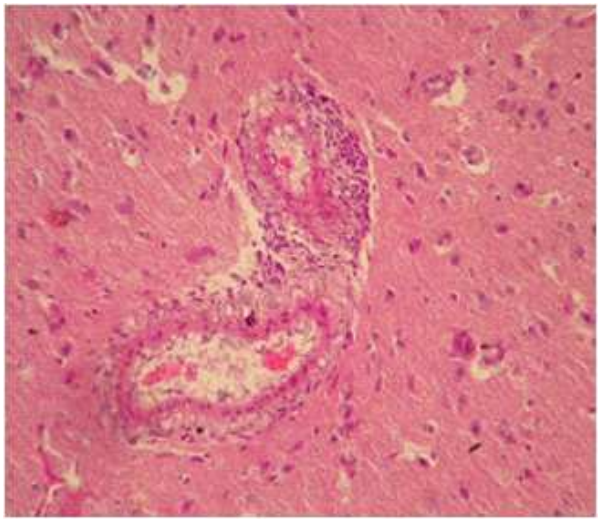

Photo 3 - Section of brain showing perivascular edema, necrosis and satellitosis. HE x 200.

C and D revealed significant reduction in the levels of Hb, PCV and TEC (Table1). Remarkable reduction of hematocrit values were observed 24 hr post dosing of meloxicam. This finding is substantiated by the fact that the toxic metabolite of NSAID cause oxidative stress to erythrocytes leading to regenerative anemia. However, total leucocytic count did not show any significant difference in the present experiment (Table 2).

Although birds receiving meloxicam at 0.8 mg revealed elevations of leucocytic count at 24 hrs post dosing, but TLC values in all the treatment groups remained non significantly higher up to 72 hrs Absolute heterophil count was increased in groups receiving 0.4 and 0.8 mg/kg of meloxicam whereas absolute lymphocyte counts of all the treated groups were at par with the control group A. Increased leucocytic count may be attributed to hepatotoxic and nephrotoxic effect of NSAIDs. Increased leucocytic count with neutrophillia and lymphopenia due to meloxicam treatment in dogs has been previously reported (Alencar *et al*., 2002).

Table 1- Effect of different dose levels of meloxicam on haemoglobin, PCV and TEC in cockerel birds at different time intervals (n=6 in each group)

[Values are mean ± SE from 6 birds in each group]

Hrs	A	B	C	D
		Haemoglobin (g/dl)		
0	9.33 ± 0.15	9.23 ± 0.22	9.17 ± 0.17	9.30 ± 0.27
8	9.47 ± 0.15	8.80 ± 0.23	8.67 ± 0.08	8.70 ± 0.18
24	8.93 ± 0.18	8.40 ± 0.14	8.40 ± 0.15	8.70 ± 0.11
48	9.23 ± 0.16^{a}	8.60 ± 0.18^{ab}	8.27 ± 0.14^{bc}	7.83 ± 0.23^{c}
72	9.00 ± 0.12^{a}	8.53 ± 0.18^{ab}	8.10 ± 0.20^{b}	8.33 ± 0.15^{b}
		PCV (%)		
0	26.50 ± 0.89	26.00 ± 1.48	25.00 ± 1.13	27.00 ± 0.45
8	26.67 ± 0.80^{a}	26.00 ± 0.86^{ab}	23.17 ± 0.15^{bc}	22.00 ± 0.37^{c}
24	26.83 ± 0.91^{a}	22.67 ± 1.28^{ab}	24.83 ± 0.87^{ab}	20.67 ± 1.12^{b}
48	25.33 ± 0.61^{a}	20.83 ± 0.70^{c}	23.17 ± 0.60^{ab}	22.50 ± 0.43^{bc}
72	25.50 ± 0.89^{a}	22.00 ± 1.03^{b}	23.00 ± 0.77^{ab}	21.17 ± 0.60^{b}
		TEC (10^{6}/cumm)		
0	2.34 ± 0.14	2.22 ± 0.15	1.91 ± 0.06	2.00 ± 0.10
8	2.06 ± 0.16	2.26 ± 0.07	2.02 ± 0.15	1.74 ± 0.07
24	2.06 ± 0.10^{a}	2.03 ± 0.07^{ab}	1.76 ± 0.05^{bc}	1.65 ± 0.06^{c}
48	2.12 ± 0.05^{a}	2.11 ± 0.08^{a}	2.10 ± 0.07^{a}	1.79 ± 0.08^{b}
72	2.09 ± 0.09^{a}	2.06 ± 0.09^{a}	1.85 ± 0.14^{ab}	1.55 ± 0.08^{b}

Values bearing same superscripts (a-c) in a row did not differ significantly.

A = Control; B = 0.2 mg/kg meloxicam; C = 0.4 mg/kg meloxicam; D = 0.8 mg/kg meloxicam.

Table 2- Effect of different dose levels of meloxicam on TLC, absolute heterophil and Absolute lymphocyte in cockerel birds at different time intervals (n=6 in each group) [Values are mean ± SE from 6 birds in each group]

Hrs	A	B	C	D
		TLC (10^3/cumm)		
0	26.33 ± 1.19	26.33 ± 1.38	27.83 ± 1.36	27.00 ± 0.79
8	28.25 ± 1.30	31.17 ± 1.42	32.58 ± 1.02	30.25 ± 0.72
24	27.58 ± 1.23[a]	28.83 ± 0.78[a]	28.67 ± 1.00[a]	32.42 ±0.75[b]
48	28.50 ± 0.90	30.75 ± 1.46	30.58 ± 1.15	32.17 ± 0.90
72	27.67 ± 1.39	31.17 ± 1.28	32.25 ± 1.09	32.00 ± 1.41
		Absolute heterophil count (10^3/cumm)		
0	6.67 ± 0.42	7.00 ± 0.30	6.83 ± 0.31	6.83 ± 0.48
8	6.83 ± 0.48	7.00 ± 0.58	6.83 ± 0.31	7.17 ± 0.31
24	6.17 ± 0.31[a]	6.67 ± 0.33[ab]	7.33 ± 0.33[b]	7.50 ± 0.34[b]
48	6.50 ± 0.43	6.83 ± 0.31	7.33 ± 0.33	7.83 ± 0.31
72	6.83 ± 0.48	7.83 ± 0.31	7.67 ± 0.21	8.17 ± 0.31
		Absolute lymphocyte count (10^3/cumm)		
0	18.50 ± 0.56	18.33 ± 0.67	18.50 ± 0.62	18.17 ± 0.54
8	18.17 ± 0.48	18.33 ± 0.49	18.50 ± 0.56	17.67 ± 0.33
24	18.67 ± 0.42	18.17 ± 0.48	17.50 ± 0.56	17.00 ± 0.26
48	18.50 ± 0.43	18.33 ± 0.42	18.17 ± 0.65	17.17 ± 0.48
72	18.67 ± 0.56	17.83 ± 0.40	17.67 ± 0.42	17.17 ± 0.31

Values bearing same superscripts (a-b) in a row did not differ significantly.

A = Control; B = 0.2 mg/kg meloxicam; C = 0.4 mg/kg meloxicam; D = 0.8 mg/kg meloxicam.

Biochemical studies – Results of biochemical studies in different groups at different time intervals are given in Table 3. At low dose exposure of birds with meloxicam, no significant variation was observed in the level of serum AST, ALT, uric acid and creatinine.

There was a statistical non significant increase in AST and ALT values in group B . Birds receiving higher dose levels of meloxicam in groups C and D revealed significant elevation in the levels of serum AST, ALT and creatinine (Table 3). Significant elevation in the levels of serum uric acid was observed only in group D.

This finding is substantiated by the fact that there was degeneration of hepatocytes in these groups, resulting into elevated levels of serum AST, ALT, uric acid and creatinine. Uric acid constitutes 60-80 % of total nitrogen in the urine of the birds. Hyperuricaemia in group D is suggestive of renal malfunction and confirms the histopathological observations of nephrotoxic changes in kidneys of group D in present experiment. This finding of elevated uric acid by meloxicam confirms the findings

of Alencar *et al*. (2003).

Thus a dose rate of 0.4 mg/kg could be considered as threshold value for meloxicam toxicity. Meloxicam can be safely used at 0.2 mg/kg body wt. in birds.

Table 3- Effect of different dose levels of meloxicam on serum uric acid, creatinine, AST and ALT in cockerel birds at different time intervals (n=6 in each group)

[Values are mean ± SE from 6 birds in each group]

Hrs	A	B	C	D
		Serum uric acid (mg/dl)		
0	6.72 ± 0.35	6.02 ± 0.39	6.38 ± 0.48	6.74 ± 0.45
8	6.36 ± 0.22^{a}	6.82 ± 0.35^{a}	6.98 ± 0.50^{a}	9.69 ± 0.41^{b}
24	6.17 ± 0.32^{a}	6.57 ± 0.36^{a}	6.62 ± 0.31^{a}	8.00 ± 0.34^{b}
48	6.91 ± 0.26	5.23 ± 0.71	6.48 ± 0.38	6.68 ± 1.20
72	6.82 ± 0.21	6.02 ± 0.28	5.76 ± 0.35	6.07 ± 0.30
		Serum creatinine (mg/dl)		
0	0.47 ± 0.03	0.55 ± 0.07	0.51 ± 0.04	0.60 ± 0.06
8	0.57 ± 0.02^{a}	0.51 ± 0.04^{a}	0.86 ± 0.03^{b}	1.12 ± 0.10^{c}
24	0.57 ± 0.04^{a}	0.57 ± 0.05^{a}	0.87 ± 0.03^{b}	1.15 ± 0.09^{c}
48	0.61 ± 0.03^{a}	0.60 ± 0.05^{a}	1.16 ± 0.07^{b}	1.22 ± 0.01^{b}
72	0.62 ± 0.04^{a}	0.61 ± 0.05^{a}	1.08 ± 0.09^{b}	1.25 ± 0.11^{b}
		Serum AST (IU/L)		
0	58.46 ± 1.62	56.92 ± 1.24	55.94 ± 1.76	59.23 ± 1.61
8	60.20 ± 2.45^{a}	67.81 ± 4.82^{a}	70.02 ± 3.19^{a}	92.88 ± 2.71^{b}
24	56.63 ± 3.12^{a}	61.57 ± 4.76^{a}	70.33 ± 3.83^{a}	111.02 ± 2.04^{b}
48	58.02 ± 2.48^{a}	65.95 ± 5.46^{a}	74.18 ± 4.12^{a}	122.26 ± 4.72^{b}
72	71.15 ± 1.72^{a}	77.50 ± 4.65^{a}	82.41 ± 1.91^{a}	97.50 ± 3.35^{b}
		Serum ALT (IU/L)		
0	30.07 ± 2.48	31.91 ± 2.04	32.50 ± 2.15	33.41 ± 1.75
8	36.16 ± 3.48^{a}	37.08 ± 2.70^{a}	45.99 ± 2.05^{a}	51.13 ± 2.58^{b}
24	36.10 ± 2.87^{a}	40.69 ± 2.88^{ab}	51.07 ± 2.33^{b}	63.15 ± 2.39^{c}
48	37.43 ± 1.79^{a}	44.93 ± 2.80^{a}	60.55 ± 1.54^{b}	64.74 ± 4.19^{b}
72	41.23 ± 2.03^{a}	38.73 ± 2.17^{a}	44.72 ± 3.05^{a}	59.27 ± 2.72^{b}

Values bearing same superscripts (a-c) in a row did not differ significantly.

A = Control; B = 0.2 mg/kg meloxicam; C = 0.4 mg/kg meloxicam; D = 0.8 mg/kg meloxicam.

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REFERENCES :

Alencar, M.M.A., Pinto, M.T., Oliveira, D.M., Pessoa, A.W., De, P., Candido, I.A., Gomes, C.V., Coelho, H., De, S.M. and Roch, M.F.G. (2002). *Ciencia-Animal*, 12(1):25-33.

Alencar, M.M.A., Pinto, M.T., Oliveira, D.M., Pessoa, A.W., De, P., Candido, I.A., Virginio, C.G., De, S.M., Roch, M.F.G., De, S. and Coelho, H. (2003). *Ciencia-Rural*, 33 (3): 525-532.

Aydin, G., Gokcimen, A,. Cicek, E., Karahan, N. and Gokalp, O. (2003). *Turk. J. Vet. Anim. Sci*., 27: 1131-1140.

Bhaumik, A., Sharma, M.C. and Lal, S.B. (1995). *Indian J. Anim. Sci.*, 65(2): 183-185.

Gupta, B.K., Misraulia, K.S., Garg, U.K., Sharma, R.K., Gopala Reddy, A. and Patel, D. (2000). *Indian J. Vet. Pathol.*, 24:49-50.

Hedau, M., Bhandarkar, A.G., Raut, S.S. Sirothia, K. (2008). *Indian J. Vet. Pathol.*, 32(2):263-266.

Luna, A.G. (1968). Manual of histopathological staining methods of Armed Forced Institute of Pathology, 3rd Edition, Mc Graw Hill Book Co., London, 124-125.

Mohapatra, D., Misra, S.C., Parija, S.C. and Misra, S.N. (1993). *Indian Vet. J.*, 70: 914-916.

Mohapatra, D., Parija, S.C., Kundu, A.K. and Misra, S.N. (1994). *Indian J. of Poult. Sci.*, 29(2):191-193.

Snedecor, G.W. and Cochran, W.G. (1994). Statistical Methods, 8th Edn., Oxford & IBH Publ.Co., New Delhi.

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