International Journal of Life science & Pharma Research

PHARMACOKINETIC AND PHARMACODYNAMIC INTERACTION BETWEEN LUMIRACOXIB AND FLUVASTATIN

JAYARAMAN ANBU*[1], ASHWINI ANJANA[1], C. ROOSEWELT[1], G. SRINIVASA RAO[1] AND R. SATHISH[2]

[1]Department of Pharmacology and Toxicology, School of Pharmaceutical Sciences, (VISTAS) Vels University, Pallavaram, Chennai-600117 India
[2]Department of Toxicology, NIS, Tambaram, Chennai-600044, India

ABSTRACT

The present study was carried out to investigate the pharmacokinetics and pharmacodynamic interaction between Lumiracoxib (20mg/kg p.o.) and Fluvastatin (5mg/kg p.o.) alone and their combination in rats by open labeled parallel study design. The animals were maintained on a standard laboratory conditions and were divided into 3 and 6 groups for Pharmacokinetic and Pharmacodynamic studies respectively.

Key words: Lumiracoxib, Fluvastatin, COX-2 inhibitors, Rheumatoid arthritis, Hypolipidemic.

1. INTRODUCTION

Rheumatoid arthritis is a chronic, systemic, inflammatory disease predominantly affecting joints and periarticular tissues and still remains a formidable disease being capable of producing severe cripping deformities and functional disabilities. Among the NSAIDs, the Cox-2 inhibitors are well tolerable by patients (Satoskar RS et al. 2001). Inhibition of cyclooxygenase (COX), the enzyme responsible for the biosynthesis of the prostaglandins and certain related autacoids, generally is thought to be a major facet of the mechanism of NSAIDs. The mechanisms by which varying NSAIDs interfere with prostaglandin synthesis then are outlined. The first enzyme in the prostaglandin synthetic pathway is prostaglandin endoperoxide synthase, or fatty acid cyclooxygenase. This enzyme converts arachidonic acid to the unstable intermediate s PGG2 and PGH2. It is now appreciated that there are two forms of cyclooxygenase, termed cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Vane J R et al. 1998). COX-1 is a constitutive isoform found in most normal cells and tissues, while COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators (Seibert K et al. 1997). However, COX-2 also is constitutively expressed in certain areas of kidney and brain (Brater DC. 1999; Goudie AC et al. 1978). Lumiracoxib or 2-[2-fluoro-6-chlorophenyl) amino]-5-methyl-benzenacetic acid is a distinct cyclooxygenase-2 selective inhibitor, which has been developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain, is chemically distinct from the other coxib in that it lacks a sulfur-containing moiety and possesses a carboxylic group that confers weakly acidic properties (pKa 4.7) (Giuseppe Carlucci. 2009). Most of the evidence supports the role of cytochrome p450 (cyp) isoenzymes in many of these drug interactions (Campbell NRC et al. 1992). The statins constitute a group of hypolipidemic agents that lower cholesterol by promoting reduction in plasma levels of LDL cholesterol (Benet L and Hoener B, 2002). The co administration of fluvastatin with certain nonsteroidal anti-inflammatory agents may increase the frequency and severity of adverse drug

reactions associated with this class of drugs, such as gastritis and nephrotoxicity (Sandra L Beaird. 2000). Inhibitors of CYP2C9, fluvastatin may cause an increase in serum coxib concentrations (William R Garnett. 2001).

2. MATERIALS AND METHODS

2.1. Reagents and chemicals

Acetonitrile (HPLC grade), Potassium dihydrogen phosphate (HPLC grade), Water (HPLC grade) - obtained from milli-Q system, Sodium chloride (AR Grade) – S.D fine chemicals, Sodium hydroxide (AR Grade)- S.D fine chemicals, Fluvastatin (CEEAL Laboratories, India) and Lumiracoxib (sun pharma, India) were obtained as gift sample.

2.2. Animals

Male wistar rats weighing about 200-220gms were selected and kept under standard laboratory conditions. The animals were allowed free access to standard pellet diet and water *ad libitum*. The blood samples were drawn after application of topical lignocaine anesthesia to minimize pain to the animals. This study protocol was approved by the Institutional Animal Ethics Committee (IAEC).

2.3. Study design

The male wistar rats (200-250g) were randomly divided into three and six groups consisting of six animals for pharmacokinetic and pharmacodynamics study respectively

2.3.1. For pharmacokinetic study, animals are treated as follows

Group I: 20mg / kg / p.o. Lumiracoxib alone dispersed in 0.25% Na CMC once a day, Group II: 5mg/kg/ p.o. Fluvastatin alone dispersed in 0.25% Na CMC once a day, Group III: Lumiracoxib 20mg/kg/p.o. and Fluvastatin 5mg/kg/p.o. concomitantly once/day.

2.3.2. For pharmacodynamic study, animals are treated as follows

Group I: 10mg / kg / p.o. Lumiracoxib alone dispersed in 0.25% Na CMC once a day in adjuvant induced arthritic rats, Group II: 2mg/kg/ p.o. Fluvastatin alone dispersed in 0.25% Na CMC once a day in Hyperlipidemic rats, Group III: Fluvastatin 2mg/kg/p.o. and Lumiracoxib 10mg/kg/p.o. concomitantly in adjuvant induced arthritic rats, Group IV: Fluvastatin 2mg/kg/ p.o. and Lumiracoxib 10mg/kg/p.o. concomitantly in Hyperlipidemic rats, Group V: Hyperlipidemic rats served as control group with (10ml/kg i.p) normal saline solution, Group VI: Adjuvant induced arthritic rats served as control group with (10ml/kg i.p) normal saline solution.

2.4. Collection of blood sample

On 1st and 8th day, blood samples of 0.5mL were drawn at 0, 0.5,1,2,4,6,8 and 24hrs and equal amount saline was administered to replace the blood volume for every blood withdrawal (Lise A Eliot and Fakhreddin J, 1999). Blood samples were drawn through retero orbital sinus into the effendraff tube. Serum was obtained by immediate centrifugation of blood samples. Centrifugation was performed by using REMIULTRA cooling centrifuge at 2500-3000rpm for 5min. All samples were stored at -4°c until pharmacokinetic and pharmacodynamics measurements are carried out.

2.5. Method of analysis

Rat plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of methanol for each 0.5 ml of plasma. After centrifugation the methanol was transferred into a clean tube. The precipitate was resuspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the methanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted with 200 µ1 of 35 % of acetonitrile and 65% of ammonium acetate buffer mobile phase was injected for HPLC analysis.

2.6. Statistical analysis

Data were expressed as mean ±SEM (n=6) for statistical evaluation of data. One-way ANOVA and student t-test were performed by using PRISM PAD statistical software program.

3. RESULTS AND DISCUSSION

3.1. Simultaneous Assay of Lumiracoxib and Fluvastatin by RP-HPLC method

Under the chromatographic conditions described above the retention times of Lumiracoxib and

Fluvastatin were found to be 16.9 and 6.8 minutes respectively.

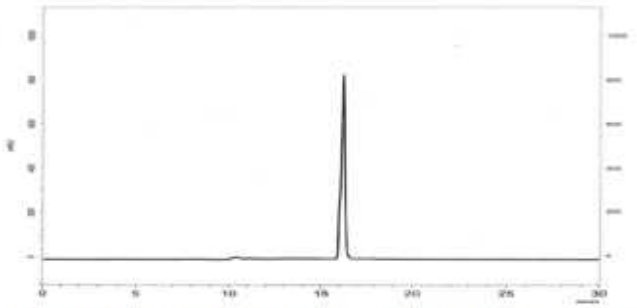

Figure 1: *Typical chromatogram of Lumiracoxib*

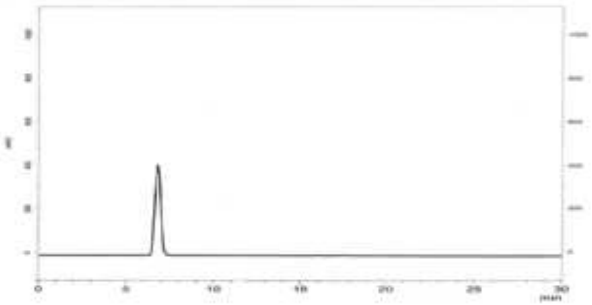

Figure 2: *Chromatogram of Fluvastatin*

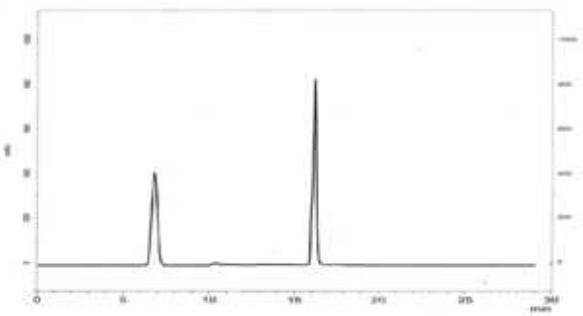

Figure 3: *Chromatogram of Lumiracoxib and Fluvastatin*

The recoveries of samples from rat plasma were found to be 94.21-108.77% at the concentration range of 20-800µg ml^{-1}, Lumiracoxib and Fluvastatin was 84.38-102.10% at the concentration of 5-35µg ml^{-1} respectively.

Table 1: ***Absolute Recovery of Determination of Fluvastatin and Lumiracoxib in Rat Plasma***

Concentration (µg / ml)		*Absolute Recovery (%)*			
Lumiracoxib	*Fluvastatin*	*Lumiracoxib*		*Fluvastatin*	
		Mean ±S.D (n = 3)	*Range (min - max)*	*Mean ±S.D (n = 3)*	*Range (min - max)*
50	5	98.79±3.92	94.21-99.24	90.42±2.03	84.38-92.17
100	10	99.53±2.61	97.00-99.88	100.18±1.96	95.26-103.24
150	15	98.73±2.89	95.28-99.85	100.29± 2.73	98.89-104.26
200	20	98.73±2.89	94.57-99.00	90.35±1.79	88.53-94.56
250	25	99.83±0.58	98.34-99.90	101.085±1.69	99.19-101.38
300	30	99.00±3.36	96.62-99.89	98.26±1.57	97.02-100.00
350	35	100.96±1.76	99.18-102.16	99.14±1.99	98.37-102.10
400	40	100.22±0.61	97.74-108.77	98.17±1.04	96.28-99.88

Values are expressed as Mean ± S.E.M.; (n=3); (*P<0.05)

To determine the linearity and the detection range of the HPLC method, samples spiked with seven different concentrations. No discernible peaks were observed within the time frame in which Lumiracoxib and Fluvastatin were detected. In the HPLC assay for the simultaneous quantification of Lumiracoxib and Fluvastatin, recovery, sensitivity and linearity were satisfactory in the concentration range studied. The slope, intercept and correlation co efficient for Fluvastatin was found to be 4235.2x + 1621.6 and R^2 = 0.9972, whereas for Lumiracoxib it was 81969x + 2951.9, R^2 = 0.9981 respectively.

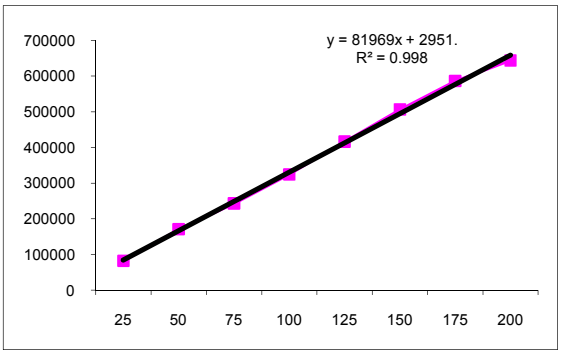

Figure 4*: Standard Calibration curve of Lumiracoxib*

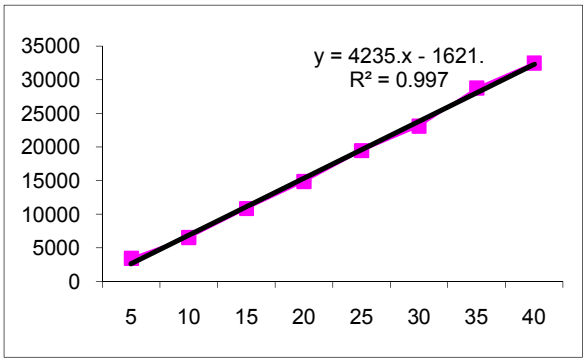

Figure 5*: Standard calibration curve of Fluvastatin*

3.2. Pharmacokinetic interaction study

In the present study, the mean plasma concentration of Lumiracoxib and Fluvastatin alone and in combination were studied and the data were presented. It was observed that administration of Lumiracoxib alone in rats for one week the plasma concentration was rapidly increased. But there was no significant alteration was noted in Fluvastatin concentration. In the combinational treatment, the Lumiracoxib peak plasma concentration was achieved after two hours after administration on day 1 and day 7 also. But on the 7^{th} day peak plasma concentration of LCB was significantly ($P<0.01$) increased to 56.43 ± 3.00 from 43.25±3.22 after 1-2 hours of treatment with FSN. Similarly, the fluvastatin concentration was also increased significantly ($P<0.05$) when administered simultaneously with lumiracoxib.

Table 2: ***Mean changes in concentration (µg/ml) of Lumiracoxib (20mg/kg/p.o.) and Fluvastatin (5mg/kg/p.o.) alone and in combination at different time intervals on Day 1 and Day 7 in rats.***

Time (hr)	*Lumiracoxib alone once daily*		*Fluvastatin alone once daily*		*Lumiracoxib with Fluvastatin once daily concomitantly*			
					Lumiracoxib		*Fluvastatin*	
	Day 1	*Day 7*	*Day 1*	*Day 7*	*Day 1*	*Day 7*	*Day 1*	*Day 7*
0	0.00	12.58±1.92*	0.00±0.00	0.00±0.00	0.00±0.00	10.07±1.20*	0.00±0.00	1.00±0.01

0.5	22.16±3.12	31.42±2.16*	4.77±0.39	4.01±0.05	17.60±2.20	38.43±4.28*	3.16±0.13	4.16±0.04
1	49.25±3.18	68.41±2.88*	14.88±1.24	15.47±0.05	39.18±2.79	49.12±4.10*	12.00±0.07	10.24±0.03*
2	37.72±2.42	54.17±3.20*	24.34±2.14	19.25±0.23*	43.25±3.22	56.43±3.00*	21.18±0.15	18.10±0.19*
4	20.33±1.98	32.13±2.86*	19.82±0.12	31.92±0.22*	31.71±2.85	38.10±2.97	11.06±0.22	8.29±0.08*
6	9.28±1.37	15.18±1.75*	16.22±1.37	27.42±0.17*	14.11±1.68	21.50±2.25*	8.31±0.26	9.14±0.12
8	4.05±1.02	10.11±1.02*	11.62±0.95.	19.65±0.14*	6.00±1.02	16.32±1.85*	5.00±0.1	6.00±0.10*
24	1.98±0.66	3.55±1.00	5.19±0.0.46	4.80±0.04	2.44±0.52	6.50±1.33*	1.22±0.1	4.50±0.07*

Values are expressed as Mean ± S.E.M.; (n=6); (*P<0.05); Comparison made between day1 and 7 alone and in combination.

From the Pharmacokinetic parameters studied, it was observed that the C_{max} (641.6±39.51 to 847.7 ±53.10ng/ml), AUC_{0-t} (1870.28±281.4 to 2376.9±343.8) and $T_{1/2}$ (2.42±0.20 to 3.56±0.21) of LCB were significantly (P<0.01) increased on day 7 after alone treatment. The fluvastatin alone after one-week treatment showed no alterations in any of the pharmacokinetic parameters. There was slight decrease in the clearance (Cl/f) rate of Fluvastatin in combination compared with Fluvastatin alone on day 1 and day 7 respectively. Similarly there was a slight decrease in the clearance (Cl/f) of Lumiracoxib in combination compared with Lumiracoxib alone by 4.92% on day 1and 4.6% on day 7 respectively. The half life of FSN was almost similar after alone and combination treatment on day 1 and day 7. All these changes were not statistically significant (P>0.05) in combinational drug treated group. The mean clearance (C1/F) was 75.38±11.2 and 53.09±7.46 L/h/kg, which was reduced to 62.47±9.11 and 63.20±8.27 L/h/kg upon treatment of Lumiracoxib with FSN in rats on day 1 and day 7 respectively. Volume of distribution was increased 3-6 and 2-5 fold in Lumiracoxib alone compared to Lumiracoxib with Fluvastatin group on day 1 and day 7 respectively.

Table 3: ***Pharmacokinetic changes of Lumiracoxib (20mg/kg/p.o.) and Fluvastatin (5mg/kg/p.o.) alone and after concomitant administration in rats***

Pharmacokinetic Parameter	*Lumiracoxib alone once daily*		*Fluvastatin alone once daily*		*Lumiracoxib with Fluvastatin once daily after concomitant treatment*			
					Lumiracoxib		*Fluvastatin*	
	Day 1	*Day 7*	*Day 1*	*Day 7*	*Day 1*	*Day 7*	*Day 1*	*Day 7*
C_{max} (ng/ml)	641.6±39.51	847.7±53.10*	23.12±2.8	21.1±2.2	520.1±28.12	456.2±23.64*	12.20±.2.5	18.00±2.1
T_{max} (h)	0.5±0.10	0.5±0.10	0.6±0.1	0.7±0.1	0.5±0.01	0.6±0.1	0.5±0.1	0.6±0.1
$AUC_{(0-t)}$ (ng.h/ml)	1870.28±281.4	2376.9±343.8*	84±3.3	85±3.2	1773±146.3	969±180.1*	39.2±3.0	61.3±4.0*
$AUC_{(0-\infty)}$ (ng.h/ml)	1942.40±204	2559.98±364.2*	86±3.6	73±2.9	1827±138.8	2032±156.9*	48.7±3.6	69.7±2.2*
$T_{½}$ (h)	2.42±0.20	3.56±0.21*	1.40±0.2	1.46±0.2	2.31±0.20	2.86±0.22	1.0±0.1	1.5±0.2
Cl/f (L/h)	75.38±11.2	53.09±7.46*	1.6±0.3	1.8±0.2	62.47±9.11	63.20±8.27	3.1±0.4	2.4±0.2
Vd/f (L/kg)	12.57±2.14	12.79±3.86	8.5±1.4	8.1±2.2	9.2±2.10	9.8±2.46	6.8±1.3	7.1±2.3

Values are expressed as Mean ± S.E.M.; (n=6); (*P<0.05); Comparison made between day1 and 7 alone and in combination.

3.3. Pharmacodynamic interaction study

3.3.1. Antiarthritic study

Rheumatoid arthritis is believed to be caused by a combination of abnormal biochemical stresses on the joint aid abnormal biochemical and metabolic changes in the articular cartilage most patients with arthritis are treated by primary care physicians. Control of systemic inflammation and prevention (or) slowing of disease progression are additional goals in patients with Rheumatoid Arthritis. Disease modifying antirheumatic drugs appears to have the capacity to alter the clinical course of Rheumatoid Arthritis Because of their analgesic and anti-inflammatory effects, NSAIDs are the class of medication most commonly used to treat joint pain and stiffness in patients with Rheumatoid Arthritis. The efficacy of agents that selectively inhibitor cox-2 in the treatment of the symptoms of arthritis and their lower incidence of GI-related adverse events compared with non selective NSAIDs, have been demonstrated in

several clinical studies (Riendeau D et al. 2001). The mean percentage inhibition of arthritis in Lumiracoxib alone and LCB+FSN treated groups were calculated and compared with untreated arthritis animals. The % inhibition of edema in lumiracoxib alone produced no significant activity on day 5 and 38.46% on day 10. But the combinational treatment of LCB+FSN showed 20.56 and 23.24% of inhibition after 5th and 10th day of treatment.

Table 4*: Antiarthritic efficacy of Lumiracoxib alone and in combination with Fluvastatin in arthritic rats*

Drug	Mean % changes in foot volume ± SEM		
	0 day	5th day	10th day
Arthritic Control	125.16±10.16	188±7.95	225.83±8.99
Arthritic Control	126.66±10.78[ns]	191.17±8.00[ns]	138.96±5.81[b]
LCB (10mg/kg) +FSN (5mg/kg)	121.48±9.74[ns]	149.33±8.54[b]	173.33±10.16[b]

N = 6; Values are expressed as mean ± SEM.
[a]P<0.05; [b]P<0.01 Vs. arthritic control; (One way ANOVA followed by Dunnet't' test.

The significant difference (P<0.05) between the treated groups was observed in the antiarthritic activity in rats. The range of therapeutic efficacy is about 25% less on concomitant treatment.

3.3.2. Antihyperlipidemic activity

Fluvastatin alone and combination of Lumiracoxib treated animals showed significant (P<0.05) and favorable changes in the level of total cholesterol, triglyceride, HDL and LDL after 0.5-1h of administration on day 1 & 7. The mean values versus time profiles of these parameters after fluvastatin alone and combinational treatment on hyperlipidemic and non-hyperlipidemic.

Table 5*: Mean ± S.E.M, plasma levels (µg/ml) of Lumiracoxib in hyperlipidemic Vs Non hyperlipidemic rats*

Time (hr)	Lumiracoxib in hyperlipidemic rats		Significance (p<0.05)	Lumiracoxib in non hyperlipidemic rats		Significance (p<0.05)
	Day1	Day 7		Day1	Day 7	
0	0.00±0.0	2.00±0.42	NS	0.00±0.0	0.62±0.10	S
0.5	11.2±1.00	8.80±1.14	NS	5.8±1.12	8.14±1.10	S
1	26.4±1.12	19.5±1.00	NS	11.2±1.30	11.66±1.12	NS
2	30.2±2.05	32.6±2.08	NS	20.1±3.51	18.39±2.00	S
4	28.8±1.00	25.17±2.3	NS	13.7±1.14	12.42±2.01	S
6	10.3±1.16	12.54±1.7	NS	10.3±1.22	8.77±2.50	S
8	6.20±1.10	8.36±1.18	NS	3.2±0.93	1.58±0.71	S
24	2.7±0.80	4.11±1.41	NS	0.88±0.21	0.98±0.20	S

*Values are expressed as Mean ± S.E.M.; (n=6); (*P<0.05); Comparison made between day1 and 7 of hyperlipidemic and non hyperlipidemic rats.*

Similarly mean triglycerides, high density lipoprotein, low density lipoprotein of after Fluvastatin with Lumiracoxib versus time profiles were shown in (Table-6a,b) and (Table-7a,b) on day 1 and day 7 respectively. After initiation of treatment with Fluvastatin compared with combination with Lumiracoxib single dose/day, it was observed that the combinational treatment altered these parameters from baseline in triglycerides, high-density lipoprotein, low-density lipoprotein, achieved a statistical significance with in 24 hrs (i.e. day 1).

Table 6: ***(a) Effect of Fluvastatin alone and combination with Lumiracoxib on Cholesterol and Triglycerides on day1***

Time	Cholesterol Levels (mg/dl)		Significance (P<0.05)	Triglycerides (mg/dl)		Significance (p<0.05)
	FSN	FSN+LCB		FSN	FSN+LCB	
Normal	80.12 ± 0.09	82.4± 0.08	NS	119.10 ± 0.17	121.0 ± 0.31	S
Control	192.26 ± 0.28	203.2 ± 0.41	NS	285.51 ± 0.67	274.0 ± 0.48	S
0.5	186.0 ± 0.21	189.42 ± 0.30	NS	276.3 ± 0.24	285.1 ± 0.44	S
1	170.1 ± 0.18	185.36 ± 0.37	S	249.23 ± 0.38	275.6 ± 0.08	S
2	164.72 ± 0.20	179.42 ±0.26	S	238.32 ± 0.22	266.7 ± 0.106	S
4	159.5 ± 0.17	162.11 ± 0.56	NS	201.8 ± 0.36	241.03 ± 0.19	S
6	146.2 ± 0.28	158.11 ± 0.09	S	224.0 ± 0.31	235.09 ± 0.11	S
8	148.0 ± 0.21	152.15 ± 0.66	NS	186.8 ± 0.40	226.25 ± 0.52	S
24	170.8 ± 0.29	150. 25 ± 0.27	S	188.9 ± 0.34	223.40 ± 0.45	S

Values are expressed as Mean ± S.E.M.; (n=6); (P<0.05); Comparison made between day1 and 7 fluvastatin alone and in combination.

Table 6: ***(b) Effect of Fluvastatin alone and combination with Lumiracoxib on LDL and HDL level on day1***

Time (Hrs)	Low Density Lipoprotein (mg/dl)		Significance (p<0.05)	High density lipoprotein (mg/dl)		Significance (p<0.05)
	FSN	FSN+LCB		FSN	FSN+LCB	
Normal	20.81 ± 0.15	25.10 ± 0.17	NS	31.12± 0.15	30.26 ± 0.10	NS
Control	76.23 ±0.36	84.92 ± 1.22	NS	58.09 ± 0.25	55.10 ± 0.14	NS
0.5	69.08±0.40	77.36 ± 1.16	S	50.26±0.84	57.72 ± 0.18	S
1	61.48±0.36	73.19 ± 1.02	S	54.74±0.56	63.17 ± 0.15	S
2	59.98±0.22	66.76 ± 0.88	S	59.48±2.00	65.18 ± 0.12	S
4	63.16±0.26	65.62 ± 0.91	NS	66.72±1.88	65.92 ± 0.24	NS
6	61.92±0.34	64.31 ± 0.42	NS	63.89±1.06	66.12 ± 0.52	NS
8	60.49±0.23	64.12 ± 0.54	NS	64.00±1.24	66.72 ±0 .75	NS
24	63.18±0.28	64.06 ± 0.82	NS	68.93±1.79	67.12 ± 0.81	NS

Values are expressed as Mean ± S.E.M.; (n=6); (P<0.05); Comparison made between day1 and 7 fluvastatin alone and in combination.

Table 7: ***(a). Effect of Fluvastatin alone and combination with Lumiracoxib on Cholesterol and Triglycerides on day7***

Time (Hrs)	Cholesterol Level (mg/dl)		Significance (P<0.05)	Triglyceride (mg/dl)		Significance (p<0.05)
	FSN	FSN+LCB		FSN	FSN+LCB	
Normal	119.23 ± 1.21	136.50 ± 1.18	S	141 ± 0.22	135.2 ± 0.42	S
0.5	166.00±1.32	141.42 ± 1.20	S	174.68±0.37	167.4 ± 0.27	S
1	129.36±1.24	120.5 ± 1.12	S	153.44±0.42	125.16 ± 0.34	S
2	131.49±1.29	119.4 ± 1.11	S	148.26±0.73	124.32 ± 0.21	S
4	139.96±1.31	118.54 ± 1.21	S	150.19±0.39	121.33 ± 0.85	S
6	142.48±1.36	115.34 ± 1.63	S	154.38±0.48	119.83 ± 0.72	S
8	140.77±1.39	110.42 ± 1.32	S	148.72±0.54	118 ± 0.63	S
24	141.68±1.44	106.32 ±1.33	S	158.41±0.69	116.60 ± 1.21	S

Values are expressed as Mean ± S.E.M.; (n=6); (P<0.05); Comparison made between day1 and 7 fluvastatin alone and in combination

Table 7*: (b). Effect of Fluvastatin alone and combination with Lumiracoxib on LDL and HDL levels on day7*

Time (Hrs)	Low Density Lipoprotein (mg/dl)		Significance (p<0.05)	High density lipoprotein (mg/dl)		Significance (p<0.05)
	FSN	FSN+LCB		FSN	FSN+LCB	
Normal	31.28±0.38	35.66 ± 0.21	NS	54.33±1.18	63.01 ± 0.12	S
0.5	36.11±0.43	34.92 ± 0.21	NS	58.38±1.74	64.12 ± 0.11	S
1	47.84±0.66	34.36 ± 0.31	S	57.27±1.36	64.92 ± 0.12	S
2	45.98±0.52	33.00 ± 0.89	S	55.21±1.12	65.00 ± 0.11	S
4	44.72±0.47	31.32 ± 0.81	S	56.39±0.98	65.12 ± 0.12	S
6	46.17±0.50	30.12 ± 0.53	S	56.68±0.98	65.36 ± 0.14	S
8	43.63±0.48	29.72 ± 0.42	S	59.41±1.08	65.50 ± 0.12	S
24	47.18±0.39	29.62 ± 0.40	S	58.48±1.10	65.89 ± 1.51	S

Values are expressed as Mean ± S.E.M.; (n=6); (P<0.05); Comparison made between day1 and 7 fluvastatin alone and in combination.

Triglycerides and low-density lipoprotein were achieved peak statistical significance on day 7th similarly high-density lipoprotein level increases from baseline from day 1 to day 7. There was statistically significant difference in triglyceride, high-density lipoprotein, and low-density lipoprotein (LDL) with treatment of Lumiracoxib in hyperlipidemic group compared with non-hyperlipidemic groups. Fluvastatin is analog of 3 – hydroxy – 3 methyl glutarate lipid lowering agent. It is a hydrophobic lactone which is readily hydrolyzed to the corresponding β-hydroxy acid a potent inhibitor of HMG – COA reductase. Animal mass balance studies with HMG – COA reductase inhibitors have shown that these drugs are usually excreted in feces. This is usually not because of a lack of absorption of the drug a major portion of absorbed inhibitor and metabolites are excreted preferentially in the bile. First pass metabolism and biliary excretion can actually enhance the efficacy of the drug. Keeping active moieties in the liver and returning them through enterohepatic recirculation could prolong the action of the drug. In the present study, it has been observed that generally in all the time points there was a gradual decrease in the level of triglycerides, low density lipoprotein, from baseline were all achieved statistical significant on day 1-7 respectively.

4. CONCLUSION

The HPLC conditions were optimized to obtain an adequate separation of the eluted compounds using suitable mobile phase compositions and analytical column with reproducibility and appreciable absolute recovery. Mobile phase and flow rate selection was based on peak parameters runtime, baseline, and ease of preparation of mobile phase. The significant difference in the pharmacodynamic results between alone and combined therapy suggest that the treatment with these two drugs in hyperlipidemic and arthritic patients may give expected response only after the slight dose adjustment compared to treatment with individual drug during long term therapy. Also there is a possibility for therapeutic failure due to lumiracoxib and fluvastatin interactions in arthritic patients. The combination of therapy of lumiracoxib and fluvastatin may have clinical importance in arthritic and hypercholestremia patients with necessary dose adjustment.

5. ACKNOWLEDGEMENTS

The authors wish to thank Dr. Ishari. K. Ganesh, Chancellor, Vels University for providing the facilities necessary to carry out this research.

6. REFERENCES

1. Benet L and Hoener B. Changes in plasma protein binding have little clinical relevance. Clinical Pharmacology and Therapeutics. 2002: 71, 115-121.
2. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. Am J Med. 1999; 107: 65-70.
3. Campbell NRC, Hasinpff BB, Stalts H, Rao B and Wong NCW. Ferrous sulfate reduces thyroxin efficacy in patients with hypothyroidism. Animal of internal medicine.1992; 117: 1010-1013.
4. Goudie AC, Gaster LM, Lake AW, Rose CJ, Freeman PC, Hughes BO and Miller D. 4-(6-Methoxy-2-naphthyl) butan-2- one and related analogues, a novel structural class of anti-inflammatory compounds. J Med Chem. 1978; 21: 1260-1264.
5. Giuseppe Carlucci. Analytical Procedure for Determination of Cyclooxygenase-2 Inhibitors in Biological Fluids by High Performance Liquid Chromatography: Review Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry. Bentham Science Publishers Ltd. 2009: 8, 22-37.
6. Lise A Eliot and Fakhreddin J. Pharmacokinetics and pharmacodynamics of nifedipine in untreated and atorvastatin treated hyperlipidemic rats. J Pharmacol Exp Thera. 1999; 291: 188-193.
7. Riendeau D, Percival MD, Berideau C, Charleson S, Dube D, Ethier D, Falgueyret JP, Friesen RW, Gordon R, Greig G, Guay J, Mancini J, Ouellet M, Wong E, Xu L, Boyce S, Visco D, Girard Y, Prasit P, Zambani R, Rodger IW, Gresser M, Ford-Hutchinson AM, Young RN and Chan CC. Etocoxib (MK-0663) preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. J pharmacol Exp Thera. 2001; 296, (2): 558-566.
8. Sandra L Beaird. CYP3A4-mediated interactions with HMG-CoA Reductase Inhibitors. J Ame pharmac Assoc. 2000; 40 (5): 637-644.
9. Satoskar RS, Bhandarkar SD and Ainapure SS. IN Pharmacology and pharmacotherapeutics. 17th Edition. Popular Prakashan Publication, Mumbai Section; 2001: 15, 1011.
10. Seibert K, Zhang Y, Leahy K, Hauser S, Masferrer J and Isakson P. Distribution of COX-1 and COX-2 in normal and inflamed tissues. Adv Exp Med Biol. 1997; 400: 167-170.
11. Vane J R, Bakhle Y S and Botting R M, Cyclooxygenases 1 and 2 Annul Rev: Pharmacol Toxicol. 1998; 38: 97-120.
12. William R Garnett. Clinical implications of Drug Interactions with Coxib. Pharmacotherapy; 2001: 21 (10), 1223-1232.