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Potential pharmacodynamic drug-drug interaction between concomitantly administered lisinopril and diclofenac sodium: a call for appropriate management in hypertensive osteoarthritic patients

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Abstract

Background: The present study was designed as an open label, multiple-dose, randomized, parallel trial to evaluate the pharmacodynamic drug-drug interaction of lisinopril and concomitantly administered diclofenac sodium in non-diabetic and diabetic, mild to moderate hypertensive, osteoarthritic patients.

Methods: Post-screening and on inclusion, patients were put on a 2-week washout period and then randomly assigned to either only lisinopril 10 mg or combination of lisinopril 10 mg and diclofenac sodium 100 mg treatments for 8–12 weeks in diseased states of hypertension and osteoarthritis with or without type 2 diabetes mellitus.

Results: The blood pressure (BP) control with lisinopril was reduced by concomitantly administered diclofenac sodium in non-diabetic (SBP: p=0.00002; DBP: p=0.000008) and diabetic (SBP: p=0.002; DBP: p=0.001) patients when compared with the patients receiving lisinopril alone. Insulin sensitivity was improved (p=0.00002) and urinary albumin excretion rate was better controlled (p=0.0096) in lisinopril-treated patients when compared with the combination treatment in diabetic pool. Serum creatinine levels increased significantly in non-diabetic patients (p=0.00004) receiving combination treatment. In addition, creatinine clearance (CLCR) and blood urea nitrogen (BUN) were significantly higher in diabetic (CLCR: p<0.00001; BUN: p=0.0098) as well as in non-diabetic (CLCR: p<0.00001; BUN: p=0.03) patients treated with combination treatment. The alterations in serum electrolytes, reduction in % platelet aggregation activity and improvement in lipid profile was more profound with combination treatment in comparison to lisinopril alone.

Conclusions: The antihypertensive efficacy and insulin sensitivity improving property of lisinopril along with the renal function might get worse in hypertensive osteoarthritic patients receiving concomitant treatment of oral diclofenac sodium with lisinopril. In addition to this, close monitoring of serum electrolytes is also suggested to rule out any long-term detrimental effect.

Keywords: diclofenac sodium; hypertension; lisinopril; osteoarthritis; type 2 diabetes mellitus.

Introduction

Hypertension is the recognized risk factor and one of the leading causes for the increasing rates of cardiovascular mortality and morbidity (1). The concordance of hypertension and diabetes is increasing day by day with a higher disproportion of hypertension in the diabetic population (2). Patients having elevated blood pressure (BP) are 2.5 times more likely to develop diabetes mellitus within 5 years (3, 4), especially type 2 diabetes mellitus (T2DM) (5). Angiotensin converting enzyme inhibitors (ACEIs) are frontline agents used for the treatment of hypertension or coexisting diabetes and hypertension to prevent or to delay cardiovascular diseases. Along with the angiotensin receptor blockers, ACEIs are drug of choice in the pharmacotherapy of type 2 diabetic patients with chronic kidney disease (CKD), because these agents delay the deterioration in glomerular filtration rate (GFR) and the worsening of albuminuria (1).

Osteoarthritis is one of the most common and highly prevailing non-inflammatory degenerative joint diseases (6). Besides paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) are frontline agents and widely used non-opioid analgesics for the treatment of osteoarthritis (7–9). Representing familiar comorbid conditions, hypertension (with or without diabetes mellitus) and osteoarthritis are common conditions that increase in prevalence with age and often coexist in the same patients (7, 10). The past few decades have witnessed many changes in the pharmacotherapy of hypertension (or coexisting diabetes mellitus) and osteoarthritis. Potentially hazardous drugs with intolerable side effects or drug-drug interactions in multiple drug therapy lead to the use of safer and better tolerated drug combinations. Coexisting diseased state of hypertension (with or without diabetes mellitus) and osteoarthritis have lead to concomitant administration of NSAIDs and antihypertensive medications (11).

Previous studies have revealed that NSAIDs attenuate the efficacy of antihypertensive medications by increasing the

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BP through several mechanisms. One of the most important mechanisms is salt and water retention by inhibition of cyclooxygenase (COX) mediated prostaglandin (PG) production in the renal arteries and increased antinatriuretic effect (COX-2 mediated) in macula densa of kidney (7, 12). Another important mechanism involved is the increased peripheral vascular resistance by inhibiting vasodilatory PGs and by potentiating vasoconstricting endothelin-1 (ET_1) (7). NSAIDs attenuate the antihypertensive effect or increase the BP in patients simultaneously taking ACEIs. Such pharmacodynamic drug-drug interactions have been reported several studies involving NSAIDs such as rofecoxib, aspirin, indomethacin, ibuprofen, diclofenac, celecoxib or piroxicam and ACEIs (13–19). The pharmacological effects of PGs (12, 20, 21) and ACEIs (14, 22, 23) on renal function are shown in Tables 1 and 2, respectively.

Diclofenac sodium, a NSAID, is a potent inhibitor of PG and thromboxane synthesis via non-selective inhibition of the COX enzymes, COX-1 and COX-2 (24). Lisinopril, lysine analog of enalaprilat, is an inhibitor of angiotensin converting enzyme (25). Tabular representations of the mechanism, pharmacodynamics and pharmacokinetic properties of lisinopril (25) and diclofenac sodium (24, 26, 27) are described in Table 3. In addition to ramipril and enalapril, lisinopril is one of the most frequently used ACEI in hypertension with or without coexisting diabetes mellitus. Also, apart from paracetamol and topical NSAIDs, oral NSAIDs including diclofenac are frequently used drugs in osteoarthritis patients at their lowest effective doses (6–9, 28). Oral diclofenac is often co-prescribed with ACEIs. Therefore, the present study was designed to address the pharmacodynamic drug-drug interaction between diclofenac and lisinopril taken concomitantly in hypertensive arthritic patients (with or without T2DM) by evaluating parameters such as BP, insulin sensitivity, platelet aggregation, renal function, serum electrolytes levels, lipid profile and hepatic function.

Materials and methods

Study design

The present study was an open label, multiple-dose, randomized, parallel group trial in patients with mild to moderate essential hypertension and osteoarthritis with or without T2DM. The protocol of the study was approved by an independent Ethics Committee, which was formed in compliance with the ICH-GCP guidelines. Written informed consent was obtained from each of the patients or the patient's relative prior to initiation of the study. The study was conducted in compliance and accordance with the ethical principles that have their origin in the Declaration of Helsinki and ICH-GCP guidelines.

Patients

A total of 81 eligible outpatients of both sexes were aged between 40 and 70 years with mild to moderate essential hypertension (diastolic BP of 95–114 mm Hg) and osteoarthritis. Patients included were without histories of coronary insufficiency, myocardial infarction, congestive heart failure, moderate renal impairment or failure (i.e., serum creatinine <133 μmol/L) and cerebrovascular accident or without gross abnormalities in routine hematological and biochemical parameters at the time of enrollment. Hypertensive osteoarthritic patients (with or without T2DM) recruited were visiting the outpatient department (OPD) of Pramukhswami Healthcare and Research Center, Ahmedabad, India.

At the time of screening, patients were excluded if they had secondary or severe hypertension, joint disorders other than osteoarthritis or history of chronic skin rash. Female patients required were non-pregnant, non-lactating or not susceptible to pregnancy (i.e.,

Table 1 Pharmacological effects of PGs on renal function (12, 20, 21).

- Under normal hydrated state: do not play major role in sodium and water homeostasis
- Under decreased renal perfusion state: by virtue of vasodilating property, increase the renal blood flow and hence GFR leading to secretion of BUN and S_{cr}; PGE_2 and PGE_2: counteract the effects of ADH in the collecting duct and thick ascending loop of Henle along with the decreased chloride (sodium) absorption in loop of Henle leading to reduced salt/water reabsorption; PGI_2: inhibit the production of renal endothelin 1 in the renal vasculature and hence decrease sodium and water reabsorption; and PGI_2: by increasing renin secretion and hence activation of RAAS induces hypokalemia

PG, prostaglandin; GFR, glomerular filtration rate; ADH, anti-diuretic hormone; BUN, blood urea nitrogen; S_{cr}, serum creatinine; RAAS, rennin-angiotensin-aldosterone system.

Table 2 Pharmacological effects of ACEIs on renal function (14, 22, 23).

By blocking ACE, ACEIs perform two functions:

- Inhibition of Ag II production: vasodilation leading to decreased peripheral vascular resistance and hence decrease in BP due to rapid pressor response; inhibit the aldosterone secretion leading to blockage of water and sodium retention and hence decrease in BP due to slow pressor response; and attenuate or reduce vascular and cardiac hypertrophy, hyperplasia and remodeling by slowing or preventing morphologic changes
- Increase the levels of bradykinin by inhibiting its degradation: stimulation of vasodilatory mediators such as PG, EDRF and NO synthesis

ACE(I), angiotensin converting enzyme (inhibitor); Ag II, angiotensin II; BP, blood pressure; PG, prostaglandin; EDRF, endothelium-derived relaxing factor; NO, nitric oxide.

Table 3 Mechanism, pharmacodynamics and pharmacokinetic properties of lisinopril and diclofenac sodium.

Parameters	Lisinopril (25)	Diclofenac sodium (24, 26, 27)
Mechanism of action	Suppression of RAAS through inhibition of ACE by blocking the conversion of Ag I to Ag II; block the degradation of vasodilator peptide bradykinin	Inhibition of PG biosynthesis via non-selective inhibition of COX isozymes
Pharmacodynamics	Reduction of both supine and standing BP in hypertensive patients; reduction in peripheral resistance in essential hypertensive patients; no rapid increase in BP on abrupt withdrawal; onset of hypertensive activity: 1 h post-dose; peak hypertensive activity: 6 h post-dose; antihypertensive effect seen for 24 h with mean antihypertensive effect at 6 h post-dose is higher than at 24 h post-dose; antihypertensive efficacy lower in black patients than in non-black patients	NSAID that exhibits anti-inflammatory, analgesic and antipyretic activities; also appears to reduce intracellular concentrations of free arachidonate in leukocytes, perhaps by altering the release or uptake of the fatty acid
Peak serum concentrations	Within 7 h post-dose	Within 2–3 h post-dose
Oral bioavailability	25%	50%
Metabolism	Does not undergo metabolism	Metabolized in liver by a cytochrome P450 isozyme of the CYP2C subfamily to 4-hydroxydiclofenac (principal metabolite) and other hydroxylated forms
Excretion	Unchanged in urine	After glucuronidation and sulfation, the metabolites are excreted in the urine (65%) and bile (35%)
Half-life	12 h	Terminal half-life of unchanged diclofenac: 2 h
Food effect	No effect	No significant effect on the extent of absorption of diclofenac, but usually delays the onset of absorption of 1–4.5 h and a reduction in peak plasma levels of <20%
Special populations	In geriatric patients, serum concentrations and AUC were higher compared with elder patients	In hepatic insufficient patients, dose is reduced as hepatic metabolism account for almost 100% elimination.

RAAS, rennin-angiotensin-aldosterone system; ACE, angiotensin converting enzyme; Ag (I/II), angiotensin (I/II); PG, prostaglandin; COX, cyclooxygenase; BP, blood pressure; NSAID, non-steroidal anti-inflammatory drugs.

surgically sterile, or on a reliable contraceptive measure or attained menopause for 1 year). Patients were also excluded if they were on an ACEI in the past or at the time of enrolment or had hypersensitivity to ACEIs, aspirin or other NSAIDs.

Patients with T2DM were on oral hypoglycemics for ≥2 years before enrolment into the study. For osteoarthritis, patients were receiving symptomatic treatment on "whenever required" basis. All antihypertensive drugs and NSAIDs were discontinued at the time of enrollment for the study. Diagnosis of essential hypertension was based on a family history of high BP and the absence of reversible causes as assessed by appropriate screening test(s).

Study methodology

Before initiation of the study, the health status of each patient was evaluated on the basis of history and physical examination, with special emphasis on examination of the cardiovascular system and other organs commonly damaged by hypertension. Initial laboratory tests included complete blood count, serum electrolyte levels, blood urea nitrogen (BUN), serum creatinine (S_{cr}), creatinine clearance (CLCR), fasting blood sugar, lipid profile [serum cholesterol (Chol.), serum triglycerides (TGs), serum high-density lipoprotein (HDL), serum low-density lipoprotein (LDL), LDL/HDL ratio, Chol./HDL ratio], serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxaloacetate transaminase (SGOT). The clinical history of each patient including BP recordings, previous disease histories, drug regimen and other positive symptoms were documented in case report forms (designed according to regulatory requirements). All patients were asked to continue their routine food habits. After a 2-week washout period, each patient was randomly assigned to one of the treatment groups as detailed in Table 4.

Supine BP and heart rates were measured twice at each visit, and the mean of two BP recordings was recorded. Supine measurements were made after the patient was recumbent for 5 min. All measurements were made on the same arm, usually the right. All the parameters were recorded before and after the treatment (8–12 weeks). At the end of treatment, study medications were discontinued and patients received advice about optimum therapy and lifestyle modifications.

Table 4 Study medications and their duration.

Group	Diseased state	n	Gender	Study drugs dose/day	Duration of therapy
1	Hypertension and osteoarthritis	23	M: 14, F: 9	Lisinopril 10 mg	8–12 weeks
2	Hypertension and osteoarthritis	24	M: 8, F: 16	Lisinopril 10 mg+ diclofenac sodium 100 mg	8–12 weeks
3	Hypertension, osteoarthritis and diabetes mellitus	17	M: 9, F: 8	Lisinopril 10 mg	8–12 weeks
4	Hypertension, osteoarthritis and diabetes mellitus	17	M: 9, F: 8	Lisinopril 10 mg+ diclofenac sodium 100 mg	8–12 weeks

n, number of subjects; M, male; F, female.

Sample analysis

The blood samples were collected by venipuncture. In each sampling, 10 mL of blood was collected. The blood was transferred into a clean dry centrifuge tube immediately after each draw. Serum was separated by centrifuging at 1006×*g* for 15 min. It was stored in clean and dry serum collection tubes at –8°C until initiation of analysis.

The blood samples were analyzed for blood sugar [glucose oxidase-peroxidase (GOD-POD) method, end point; SPAN Diagnostics Ltd., Surat, India], BUN [diacetyl monoxime (DAM) method; SPAN Diagnostics Ltd.], S_{cr} (alkaline picrate method; SPAN Diagnostics Ltd.), platelet aggregation (Optical aggregometry method; UV visible 1601-spectrophotometer, Shimadzu Corporation, India); serum sodium (flame photometry), serum potassium (flame photometry), Chol. [cholesterol oxidase-peroxidase (CHOD-POD) method; Beacon Diagnostics Pvt. Ltd., Navsari, India], TGs [glycerol phosphate oxidase (GPO) method; Pointe Scientific Inc., USA], HDL [cholesterol oxidase-peroxidase (CHOD-POD) method; Beacon Diagnostics Pvt. Ltd.], SGOT [colorimetry: 2,4-dinitrophenylhydrazine (DNPH) method; SPAN Diagnostics Ltd.] and SGPT [colorimetry: 2,4-dinitrophenylhydrazine (DNPH) method; SPAN Diagnostics Ltd.].

LDL (calculated from Friedewald's formula), LDL/HDL ratio and Chol./HDL ratio were the derived parameters. Insulin sensitivity index (K_{ITT}) was calculated according to the method of Alford et al. (29) in which estimated blood glucose was plotted against time on semi-log paper to calculate $t_{1/2}$, and the insulin sensitivity index was calculated by Eq. [1] below. CLCR was calculated using the Cockcroft-Gault equation (30–32), Eq. [2] mentioned below.

$$K_{ITT}=(0.693/t_{1/2})\times 100 \quad [1]$$

$$CLCR_{male}=[(140\text{-age})\times \text{body weight}]/(72\times S_{cr}) \quad [2]$$

(Note: the proportion of muscle mass on body weight is relatively lower in women than in men. Therefore, the calculated value of creatinine clearance was multiplied by the factor of 0.85 in female patients; age: years; body weight: kg; S_{cr}: mg/dL; CLCR: mL/min.)

Overnight urine (early morning) was collected before and after the treatment period. Urine samples were estimated for urinary albumin excretion rate (UAER; Micral test; paper chromatography; Boehringer Mannheim India Ltd., Mumbai, India).

Statistical analysis

All the results of the estimations were expressed as the mean±SEM. For all the parameters, one-way analysis of variance (ANOVA) was used to assess the differences among the treatment groups. A p-value of <5% ($p<0.05$) was considered to indicate significant differences between the means. Furthermore, 95% confidence intervals (95% CIs) were calculated for differences of means (treatment-baseline) for each parameter. Data were analyzed by the non-parametric Wilcoxon two-sample rank sum test when assumptions of parametric ANOVA were not met.

Results

Demographic parameters obtained were age, sex, height, weight, risk factors involved and underlying disease. Gender distribution along with the distribution of diabetic and non-diabetic patients in each group are shown in Table 4. The mean age of patients was 56.8 years. Among the total number of patients, 47 (58.02%), 31 (38.27%), 2 (02.48%) and 1 (01.23%) patients were living sedentary, moderate, heavy and athletic lifestyles, respectively. A total of 29 patients were suffering from obesity. Demographic and baseline characteristics of the patients included were comparable among all four groups.

Physical parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP) and biochemical parameters, namely, insulin sensitivity and UAER (in diabetic patients only), platelet aggregation, S_{cr}, CLCR, BUN, serum sodium, serum potassium, lipid profile (Chol., TGs, LDL, HDL, LDL/HDL ratio and Chol./HDL ratio), SGOT and SGPT were studied in both non-diabetic and diabetic patients. The parameter data are represented by mean differences of changes as shown in Tables 5–8.

Blood pressure

BP control was found to be adequate (i.e., DBP ≤90 mm Hg) in patients who were receiving lisinopril compared with baseline (or post-washout) values. However, the BP lowering effect of lisinopril was significantly reduced upon concurrent treatment with diclofenac sodium in both diabetic (SBP: p=0.002; DBP: p=0.001) and non-diabetic (SBP: p=0.00002; DBP: p=0.000008) patients.

Insulin sensitivity and urinary albumin excretion rate

Insulin sensitivity and UAER were studied in diabetic patients only. Insulin sensitivity was increased significantly

Table 5 The mean differences of changes (±SEM) with 95% confidence interval (CI) in the parameters studied in diabetic patients treated with lisinopril (L) and lisinopril-diclofenac sodium combination (L+D).

Parameters	L (n=17)	L+D (n=17)	p-Values	95% CI
SBP, mm Hg	–22.12±3.45	–0.41±5.38	0.002	–28.25, –15.17
DBP, mm Hg	–25.24±2.29	–13.65±2.30	0.001	–18.13, –5.05
Insulin sensitivity	0.27±0.03	0.04±0.03	0.00002	0.13, 0.33
UAER, mg/day	–22.82±3.49	–7.65±4.27	0.0096	–26.39, –3.97
% Platelet aggregation	–6.06±5.30	–37.47±3.72	0.00003	18.38, 44.44
Serum Na^+, mEq/L	–3.06±1.66	–9.06±1.60	0.014	1.37, 10.63
Serum K^+, mEq/L	0.19±0.13	0.57±0.18	0.093	–0.82, 0.06
S_{cr}, mg/dL	0.16±0.10	0.46±0.12	0.072	–0.62, 0.02
CLCR, mL/min	–5.61±1.95	–18.14±2.00	<0.0001	–22.39, –1.47
BUN, mg/dL	4.06±1.42	8.71±0.92	0.0098	–8.05, –1.25
SGOT, U/L	–1.88±1.26	1.82±1.11	0.034	–7.07, –0.33
SGPT, U/L	0.47±1.34	3.12±2.08	0.29	–7.62, 2.32

SBP, systolic blood pressure; DBP, diastolic blood pressure; UAER, urinary albumin excretion rate (mg/day×0.694=μg/min); Na^+, sodium and K^+, potassium (mEq/L×1.0=mmol/L); S_{cr}, serum creatinine (mg/dL×88.40=μmol/L); CLCR, creatinine clearance (mL/min×0.0167=mL/s); BUN, blood urea nitrogen (mg/dL×0.357=mmol/L); SGOT, serum glutamic oxaloacetate transaminase; SGPT, serum glutamic pyruvate transaminase.

Table 6 The mean differences of changes (±SEM) with 95% confidence interval (CI) in the parameters studied in non-diabetic patients treated with lisinopril (L) and lisinopril-diclofenac sodium combination (L+D).

Parameters	L (n=23)	L+D (n=24)	p-Values	95% CI
SBP, mm Hg	–21.83±2.87	–3.04±3.59	0.00002	–28.02, –9.56
DBP, mm Hg	–22.39±7.43	–9.79±9.49	0.000008	–17.58, –7.62
% Platelet aggregation	–4.04±5.00	–32.38±4.01	0.00006	15.58, 41.10
Serum Na^+, mEq/L	–4.48±0.85	–8.58±1.22	0.009	1.10, 7.10
Serum K^+, mEq/L	0.28±0.13	0.64±0.13	0.04	–0.70, –0.02
S_{cr}, mg/dL	0.08±0.05	0.53±0.10	0.00004	–0.64, –0.26
CLCR, mL/min	–7.45±0.77	–30.77±1.89	<0.0001	–34.69, –5.84
BUN, mg/dL	3.04±1.07	6.83±1.24	0.03	–7.08, –0.5
SGOT, U/L	–0.57±1.42	2.04±0.85	0.12	–5.88, 0.66
SGPT, U/L	–0.48±1.57	3.46±1.72	0.098	–8.60, 0.72

SBP, systolic blood pressure; DBP, diastolic blood pressure; Na^+, sodium and K^+, potassium (mEq/L×1.0=mmol/L); S_{cr}, serum creatinine (mg/dL×88.40=μmol/L); CLCR, creatinine clearance (mL/min×0.0167=mL/s); BUN, blood urea nitrogen (mg/dL×0.357=mmol/L); SGOT, serum glutamic oxaloacetate transaminase; SGPT, serum glutamic pyruvate transaminase.

Table 7 The mean differences of changes (±SEM) with 95% confidence interval (CI) in lipid profile in diabetic patients treated with lisinopril (L) and lisinopril-diclofenac sodium combination (L+D).

Parameters	L (n=17)	L+D (n=17)	p-Values	CI (95%)
Chol., mg/dL	11.65±11.23	–46.41±12.40	0.0015	24.48, 91.69
TGs, mg/dL	29.18±9.23	–13.47±10.14	0.004	15.08, 70.22
LDL, mg/dL	–10.24±8.18	–23.29±7.08	0.24	–8.71, 34.81
HDL, mg/dL	3.65±2.87	16.71±2.68	0.002	–20.95, –5.17
LDL/HDL ratio	–0.77±0.41	–2.35±0.36	0.007	0.48, 2.68
Chol./HDL ratio	–0.45±0.84	–4.67±0.62	0.0003	2.12, 6.32

Chol., serum cholesterol; TGs, serum triglycerides (mg/dL×0.01129=mmol/L); HDL, serum high-density lipoprotein and LDL, serum low-density lipoprotein (mg/dL×0.02586=mmol/L).

in lisinopril (p=0.00002) treated patients when compared with the patients receiving lisinopril and diclofenac sodium concurrently. Similarly, UAER was significantly decreased in lisinopril treated patients (p=0.0096) compared with patients administered lisinopril and diclofenac sodium concomitantly.

Table 8 The mean differences of changes (±SEM) with 95% confidence interval (CI) in lipid profile in non-diabetic patients treated with lisinopril (L) and lisinopril-diclofenac sodium combination (L+D).

Parameters	L (n=23)	L+D (n=24)	p-Values	CI (95%)
Chol., mg/dL	8.30±10.87	–20.75±12.16	0.083	–3.65, 61.75
TGs, mg/dL	30.52±8.96	8.42±8.10	0.07	–2.0, 46.20
LDL, mg/dL	–11.30±7.98	–28.50±7.17	0.12	–4.20, 38.60
HDL, mg/dL	2.78±2.82	11.83±3.10	0.02	–16.30, –1.80
LDL/HDL ratio	–0.65±0.42	–1.76±0.28	0.03	0.01, 2.12
Chol./HDL ratio	0.01±0.55	–2.59±0.52	0.001	1.09, 4.11

Chol., serum cholesterol; TGs, serum triglycerides (mg/dL×0.01129=mmol/L); HDL, serum high-density lipoprotein and LDL, serum low-density lipoprotein (mg/dL×0.02586=mmol/L).

Platelet aggregation

In comparison to lisinopril treated patients, platelet aggregation property (expressed as % platelet aggregation) was significantly reduced in patients receiving lisinopril and diclofenac sodium concomitantly among the diabetic (p=0.00003) as well as the non-diabetic (p=0.00006) pool.

Serum electrolytes

Serum electrolytes (serum sodium and serum potassium levels) of all the patients enrolled were found in the normal range at baseline (or post-washout). Serum sodium levels were reduced significantly in diabetic (p=0.014) and non-diabetic (p=0.009) patients receiving lisinopril and diclofenac sodium combination in comparison with lisinopril administered patients. Serum potassium levels were significantly increased in non-diabetic patients receiving lisinopril and diclofenac sodium combination (p=0.04) when compared with the lisinopril treated non-diabetic patients. However, the same significant trend (p=0.093) was not observed in the diabetic pool. Although serum sodium levels were lowered (still within the normal physiological range, i.e., 135–144 mEq/L) and serum potassium levels were raised (still within the normal physiological range, i.e., 3.6–4.8 mEq/L) in patients receiving either lisinopril or combination of lisinopril and diclofenac sodium, none of the patients developed any sign of hyponatremia (such as thirst, dry mouth, oligouria, etc.) or hyperkalemia (such as neuromuscular disturbances, bradycardia, etc.), respectively.

Effect on renal function

Renal function of the patients was studied in terms of S_{cr}, CLCR and BUN. S_{cr} levels were found within normal range at baseline (or post-washout) and remained within that range in patients receiving only lisinopril therapy. However, these levels were significantly increased (p=0.00004) in non-diabetic patients receiving diclofenac sodium-lisinopril combination when compared with those receiving the lisinopril alone which was not the case in diabetic patients. The mean differences of the increase in S_{cr} levels in non-diabetic (p=0.00003) and diabetic (p=0.07) patients receiving lisinopril and lisinopril-diclofenac sodium combination with regard to the baseline values were found as 0.45 mg/dL (95% CI: –0.64, –0.26) and 0.30 mg/dL (95% CI: -0.62, 0.02), respectively. As evident from the results, S_{cr} levels were relatively higher in non-diabetic patients compared with diabetic patients receiving diclofenac sodium concomitantly with lisinopril. Although the increase in the S_{cr} level in the non-diabetic patients was statistically significant from those in diabetic patients, it was not clinically significant as these levels remained in the physiological range.

CLCR was significantly lowered in non-diabetic (p<0.0001) and diabetic (p<0.0001) patients treated with lisinopril and diclofenac sodium when compared with lisinopril alone. The mean differences of reduction in CLCR levels in non-diabetic and diabetic patients receiving lisinopril and lisinopril-diclofenac sodium combination with regard to the baseline values were found as –23.32 mL/min (95% CI: –0.64, –0.26) and –12. 53 mL/min (95% CI: –22.39, –1.47), respectively. In addition to a statistically significant reduction in CLCR levels, data were also found to be clinically significant in both patient pools, the higher being in combination treatment than the lisinopril alone therapy.

BUN levels were significantly increased in the diabetic (p=0.0098) as well as non-diabetic (p=0.03) patients receiving concomitant treatment of diclofenac sodium and lisinopril. The mean differences of the increase in BUN levels in non-diabetic (p=0.03) and diabetic (p=0.001) patients receiving lisinopril and lisinopril-diclofenac sodium combination with regard to their respective baseline levels were found to be –3.79 mg/dL (95% CI: –7.08, –0.5) and –4.65 mg/dL (95% CI: –8.05, –1.25), respectively. Furthermore, the BUN levels were touching the upper border of the physiological range in patients receiving treatment of diclofenac sodium and lisinopril concomitantly. Hence, although these findings were not clinically significant, one may have to closely monitor the patients at regular intervals.

Effect on lipid profile

The lipid profile was studied in terms of Chol., TGs, LDL, HDL, LDL/HDL ratio and Chol./HDL ratio. In the diabetic pool, Chol. (p=0.0015), TGs (p=0.004), LDL/HDL ratio (p=0.007) and Chol./HDL ratio (p=0.0003) were significantly reduced and HDL (p=0.002) significantly increased in combination treatment when compared with the lisinopril alone. LDL was decreased in combination treatment compared

with lisinopril treatment, but no remarkable difference was observed among the two treatments.

In the non-diabetic pool, LDL/HDL ratio (p=0.03) and Chol./HDL ratio (p=0.001) were significantly reduced and HDL (p=0.02) was significantly increased in combination treatment compared with lisinopril alone. Other lipid parameters were not significantly altered in this pool of patients.

Effect on hepatic function

Hepatic function was studied in terms of SGOT and SGPT levels. Concomitant treatment with diclofenac sodium and lisinopril showed an increase in SGOT levels in non-diabetic (p=0.12) and diabetic (p=0.03) patients. Concomitant treatment with diclofenac sodium and lisinopril did not alter SGPT levels in non-diabetic (p=0.09) and diabetic (p=0.29) patients.

Discussion

To gain an insight of the prominent effects of NSAIDs on BP elevation or attenuating the BP reduction when administered concomitantly with ACEIs, the present study was carried out to investigate the interaction of ACEI, lisinopril and concomitantly administered NSAID, diclofenac sodium in non-diabetic and diabetic hypertensive osteoarthritic patients.

BP was the only physical parameter studied in the present study. Treatment with lisinopril significantly reduced both SBP and DBP in non-diabetic as well as diabetic patients. However, on concomitant treatment with diclofenac sodium, lisinopril lost BP blood control significantly.

A meta-analysis of several clinical trials has shown that aspirin counteracts the antihypertensive efficacy of enalapril and captopril at a dose of ≥300 mg/day (14). Rofecoxib significantly elevated SBP in osteoarthritic and hypertensive patients who were also under concomitant treatment with ACEIs (13). In a study involving patients under enalapril treatment, indomethacin was found to elevate BP by 10.1/4.9 mm Hg (15). In another study, hypertensive patients treated by captopril, concomitant treatment with indomethacin significantly increased 24-h mean SBP (4.2 mm Hg) and DBP (2.7 mm Hg) (16). Ibuprofen was found to increase SBP (6.5 mm Hg; p<0.001) and DBP (3.5 mm Hg; p<0.01) significantly in hypertensive patients stabilized on ACEI therapy when compared with placebo (17). In a crossover clinical trial involving hypertensive and osteoarthritic patients stabilized on ACEI therapy, a significant increase in 24 h SBP and DBP was found, where celecoxib significantly elevated BP at its peak level (18). A parallel group prospective clinical trial involving hypertensive and osteoarthritic patients receiving lisinopril and hydrochlorothiazide combination showed that ibuprofen and piroxicam elevated SBP by 7.7%–9.9% (19). According to a meta-analysis of several clinical studies, indomethacin, naproxen, piroxicam and ibuprofen caused a greater rise in BP among hypertensive patients (20).

The attenuation of the antihypertensive effect of lisinopril by diclofenac sodium observed in our study is also in agreement with the 7th Report of the Joint National Committee, 2003 (1) and the American College of Cardiology Foundation/American Heart Association 2011 Expert Consensus Document on Hypertension in the Elderly (33) which states that NSAIDs may offset BP control by ACEIs through inhibition of PG synthesis and that ACEIs increase PG synthesis. In our opinion, this PG inhibition may produce complications when aspirin is administered in higher doses or other NSAIDs at their therapeutic doses, as in the case of arthritis. Therefore, appropriate monitoring of BP is warranted during combined administration of NSAIDs and ACEIs.

Insulin resistance with consequent hyperinsulinemia, glucose intolerance and dyslipidemia, i.e., metabolic changes that represent independent risk factors for coronary heart disease, are more common in hypertensive patients than normotensive patients (34). In patients with T2DM, insulin resistance leads to poor glycemic control (impaired fasting glucose), hyperinsulinemia, hypertension, dyslipidemia and possibly other pathological conditions which are contributing factors of the metabolic syndrome (34, 35).

In the present study, insulin sensitivity was measured as glucose disposal rate, K_{ITT}, by the method of Alford et al. (29). Insulin sensitivity was significantly enhanced in patients receiving chronic treatment with lisinopril which was in accordance with the previous studies of ACEIs. The proposed mechanism behind the beneficial effects of ACEIs on improvement of insulin sensitivity and insulin secretion is through the vascular system and ionic balance. ACEIs cause vasodilation which induces improved blood circulation in skeletal muscle and pancreas leading to peripheral insulin action and promoting insulin secretion, respectively. By preserving potassium and magnesium pools with the blockade of aldosterone, ACEIs could improve cellular insulin secretion and action. Another important mechanism which has been described is the ACEI mediated inhibition of angiotensin and bradykinin enhancement which play an important role in insulin cascade signaling and increase in glucose transporter type 4 (GLUT-4) (36).

Furthermore, combining diclofenac sodium with lisinopril counteracted the enhancement of insulin sensitivity shown by lisinopril, i.e., we observed significant lowering of insulin sensitivity in diabetic patients receiving diclofenac sodium-lisinopril combination when compared with the patients receiving lisinopril alone. Chronic inflammation is an important risk factor involved in the pathophysiology of insulin resistance (30, 37). NSAIDs such as salsalate (38, 39), sodium salicylate (40) and indomethacin (41) have been reported to improve insulin resistance in clinical as well as preclinical models of T2DM. Diclofenac did not show such anti-inflammation mediated improvement in insulin resistance. Therefore, findings of our study are suggestive of the fact that patients with diabetes, hypertension and arthritis receiving long-term treatment with oral hypoglycemics, lisinopril and diclofenac sodium must be closely monitored for dose adjustments to maintain an optimal glycemic control.

CKD associated with diabetes is defined by the presence of microalbuminuria (20–200 μg/min) or macroalbuminuria (>300 μg/min) or proteinuria and occurs within 20–25 years of the onset of type 1 or type 2 diabetes in a large proportion of patients. Hypertension and diabetes are coexisting states

involved in the pathophysiology of CKD. Approximately 30% of patients with diabetic nephropathy, a chronic kidney disease, progress to end stage renal disease (ESRD) (1, 42). The control of each 10 mm Hg of SBP significantly reduces overall mortality associated with diabetic nephropathy and the progression of diabetic nephropathy to ESRD with significant reductions in proteinuria (1, 43). A meta-analysis of several clinical trials has shown that ACEIs cause significant reductions in the risk for onset and progression of nephropathy along with the increase in its regression. ACEIs are also associated with a significant reduction in the risk for all-cause mortality in patients with diabetic nephropathy (42, 44).

In the present study, UAER was reduced following chronic treatment with lisinopril in diabetic patients. This finding is in agreement with a previous study of lisinopril mediated significant reduction in the UAER in hypertensive diabetic patients (45). As reported in previous studies, NSAIDs have shown anti-proteinuric effects which are attributed to reduction in the effective renal plasma flow (ERPF) and GFR by inhibiting PGE_2 production. Also, treatment with the combination of lisinopril and indomethacin has an additive effect in reducing GFR and hence glomerular protein leakage (46–48). However, UAER was increased following treatment with diclofenac sodium and lisinopril combination. This shows the ability of diclofenac sodium to attenuate the anti-proteinuric effect of lisinopril in diabetic hypertensive and arthritic patients. Thus, the findings of our study advocate appropriate monitoring of UAER in those patients who are receiving chronic treatment with lisinopril and diclofenac sodium simultaneously.

Furthermore, we have estimated % platelet aggregation in an attempt to find the effect of lisinopril on platelet aggregation and how it is affected by co-administration of diclofenac sodium. By inhibiting ACE, ACEIs block angiotensin II as well as bradykinin dependent platelet activation and aggregation (22, 49–51). In our study, there was no significant alteration in % platelet aggregation in patients receiving chronic lisinopril treatment when compared with the values of its pretreatment (or post-washout) stage. COX-1 inhibition leads to reduced expression of prothrombotic thromboxane A_2 (TXA_2). COX-2 inhibition decreases production of PGE_2 leading to reduced vasodilation and increased platelet aggregation property. Thus, hematological risks depend on the balance between COX-1 and COX-2 mediated activities of NSAIDs (52). In the present study, % platelet aggregation was significantly reduced in patients receiving lisinopril along with diclofenac sodium when compared with those receiving lisinopril alone.

Our study suggests that patients with arthritis and hypertension with or without diabetes mellitus may benefit from concomitant use of lisinopril and diclofenac sodium as far as antiplatelet activity is concerned. Therefore, this combination may additionally be beneficial in checking cardiovascular complications. The interconnection between fibrinolysis/hemostasis, hypertension and coronary artery disease is complex and incompletely understood; however, agents which normalize platelet activity and help in maintaining hemostasis can assist in the treatment of these conditions.

Hyperglycemia and hyperinsulinemia directly affect renal tubule leading to inhibition of sodium excretion (34, 35). Also the renin-angiotensin-aldosterone pathway leads to sodium retention. By contrast, natriuresis occurs soon after initiation of ACEI therapy (53). In our study, there was no significant change in serum sodium levels following lisinopril treatment in diabetic as well as non-diabetic hypertensive patients even though there was a decrease in serum sodium levels. Fluid retention is the most common NSAID-related renal complication, occurring to some degree in virtually all exposed individuals and is readily reversible on discontinuation of the NSAID (20, 21, 52). In our study, serum sodium levels were significantly reduced in the patients receiving diclofenac sodium in addition to lisinopril. Although these observations are not clinically significant as values of serum sodium level were falling within the normal range, one cannot rule out a hyponatremic effect in the group of patients receiving long-term therapy with diclofenac sodium and lisinopril.

In addition, serum potassium level increased in patients receiving chronic lisinopril therapy when compared with the baseline values and in patients receiving chronic treatment with lisinopril plus diclofenac sodium in hypertensive patients with or without diabetes mellitus. However, none of the patients developed any sign of hyperkalemia. ACEIs are known to reduce aldosterone secretion and potassium retention is not uncommon during treatment with such agents. NSAIDs are also reported to cause hyperkalemia (25, 33, 54, 55). Our observations are in parallel with the earlier findings of hyperkalemia in patients receiving ACEIs and NSAIDs concomitantly. Thus, it could be suggested that patients must be monitored for serum potassium levels to avoid hyperkalemic complications such as fatigue, weakness, tingling, numbness, paralysis, bradycardia, palpitations or difficulty in breathing. Extracellular fluid potassium concentration is normally regulated precisely at ~4.2 mEq/L. This precise control is necessary because many cell functions are very sensitive to changes in extracellular fluid potassium concentration (56).

In addition to the above, S_{cr} and BUN levels increased significantly and CLCR levels reduced significantly in patients receiving lisinopril and diclofenac sodium when compared with those on chronic lisinopril treatment alone, with the exception of S_{cr} in patients receiving lisinopril vs. lisinopril and diclofenac combination.

The most common cause of an acute increase in S_{cr} levels with reduction in CLCR following inhibition of the renin-angiotensin system results from decreased arterial blood volume. This is due to hypoperfusion secondary to volume depletion from overaggressive diuresis, low cardiac output seen in heart failure, or both. In these clinical settings, the reduced pressure head from the afferent arteriole further lessens the already reduced intraglomerular pressure imposed by ACEIs. Thus, the compensatory elevation of single-nephron GFR seen in renal insufficiency and diabetes condition is reduced in an almost additive manner when hypoperfusion and ACE inhibition coexist. This reduction in GFR is reversible within 1 month when ACEIs are ceased, except in renal insufficient patients (57). By inhibiting COX, NSAIDs systematically reduce the production of several PGs with vasodilating effect,

including PGE_2 and PGI_2. At the renal level, inhibition of PGs results in a drop in the renal blood flow, with reduced GFR and a consequent increase in serum urea, and S_{cr} with a decrease in CLCR (20, 30, 32).

The increase in BUN and creatinine levels along with reduction in CLCR shows that GFR and blood flow to the kidneys reduced significantly in patients receiving the concomitant treatment of diclofenac sodium and lisinopril leading to deterioration of renal function. These findings are in agreement with the report of Bouvy et al. revealing an increased risk of hospitalization for renal dysfunction at the start of NSAID therapy in users of ACEIs (58).

In addition to kidney function tests, lipid profile and liver function tests were also studied. Although Chol., HDL and LDL levels did not change markedly in non-diabetic patients on chronic lisinopril treatment, Chol. as well as TG levels decreased significantly in diabetic patients receiving concomitant treatment with lisinopril and diclofenac sodium, whereas reduction in Chol. levels in non-diabetic patients receiving similar treatment were marginally significant. Furthermore, HDL levels increased significantly in both non-diabetic and diabetic patients receiving concomitant treatment with lisinopril and diclofenac sodium.

An association has been reported among insulin resistance, hypertension and abnormal lipid profile (34) with dyslipidemia, low HDL, higher TGs and elevated apolipoprotein B being the prominent features of insulin resistance and T2DM (2). Also, significant numbers of osteoarthritic patients have diabetes mellitus and hypercholesterolemia (10, 20). Previous studies have shown that lisinopril decreases Chol., TGs and LDL levels while slightly raising HDL levels in diabetic as well as non-diabetic patients (59, 60). It is also reported that ACEIs have no adverse effects on plasma lipid concentrations or on glucose tolerance (61). Total cholesterol reduction has been associated with improvements in macroalbuminuria and hence cardiovascular and renal complications. As stated earlier, ACEIs inhibit the proteinuria which can be further improved by total cholesterol control. Patients treated with salsalate have shown reduction in elevated TGs levels (39). In our study, TG levels were markedly decreased in the diabetic as well the non-diabetic pool which implies that addition of NSAID to ACEI therapy can improve triglyceride profile.

Furthermore, LDL/HDL ratio and Chol./HDL ratio were reduced significantly in both non-diabetic and diabetic patients receiving concomitant treatment with lisinopril and diclofenac sodium when compared with the patients on long-term lisinopril therapy alone. These findings suggest that the concomitant therapy with diclofenac sodium and lisinopril has a beneficial effect on lipid profile and may play an important role in checking the cardiovascular complications in patients with hypertension, diabetes mellitus and arthritis.

Liver function tests were studied in terms of SGOT and SGPT. They remained unaltered following chronic treatment with lisinopril. Combination of diclofenac sodium and lisinopril resulted in higher SGOT and SGPT levels in both non-diabetic and diabetic patients compared with those on the respective chronic treatment with lisinopril alone. The increase in SGOT levels in the diabetic patients was found to be statistically significant. Very rarely, ACEIs have been associated with a syndrome that starts with cholestatic jaundice or hepatitis and progresses to fulminant necrosis and (sometimes) death (25). It is reported that aminotransferase levels increase in approximately 15% of patients taking diclofenac sodium chronically (26). Periodic monitoring of hepatic function in the diabetic patients on diclofenac sodium along with lisinopril may help in deciding continuation of the treatment.

Following a discussion of the above findings, key issues include the use of oral NSAIDs (or diclofenac) in geriatric patients concomitantly receiving ACEIs (or lisinopril) and whether the use of topical NSAIDs is appropriate in hypertensive osteoarthritic patients. Geriatric patients have increased prevalence of cardiovascular complications with diminished renal function. Hence, prescribing a NSAID alone or in combination with an ACEI strictly requires thorough medical history check-up and monitoring at regular intervals. Patients with CLCR <50 mL/min should not be prescribed NSAIDs as they have renal PG processes blunted by selective and non-selective NSAIDs (28, 52). Topical NSAIDs are often used with the therapeutic rationale of minimizing systemic NSAID exposure, with a focus on those who have risk factors but require the therapeutic benefit of an anti-inflammatory agent. Pharmacokinetic data show that using topical diclofenac 1% gel results in a 150-fold lower peak plasma concentration and 17-fold lower mean plasma concentration of diclofenac relative to a comparable dose of oral diclofenac. Use of topical diclofenac gel is an option in hypertensive osteoarthritic patients. Limiting factors with the use of topical diclofenac gel include its evaluation without active comparator and therapeutic benefit in superficial joints of knee and hands with no supporting evidence in feet, shoulders, elbows, temporomandibular joints and deep joints such as hip and spine (28, 52).

Conclusion

In conclusion, it can be suggested from our study that chronic co-administration of oral diclofenac sodium along with lisinopril can reduce the antihypertensive efficacy of the lisinopril and may have deleterious effect on insulin sensitivity, UAER, serum electrolytes and renal function. Furthermore, the beneficial effects observed with concomitant administration of oral diclofenac sodium with lisinopril on lipid profile and % platelet aggregation can be compensated by any detrimental effects on BP, renal function and liver function in hypertensive osteoarthritic patients (with or without T2DM). In addition to this, alterations in serum electrolytes require close monitoring of the patients for any signs and symptoms of hyponatremia and hyperkalemia.

Thus, the prescribing physician should decide whether to add oral diclofenac sodium to the regimen of lisinopril considering the risks and benefits and even if oral diclofenac sodium is added, appropriate monitoring of the parameters may prevent the deleterious effect of the combination.

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