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RESEARCH ARTICLE

The Risk of Bone, Joint and Inflammatory Bowel Disorders in Patients Treated with Angiotensin-Converting Enzyme Inhibitor Drugs

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Abstract

Objective: the aim of this study is to describe the adverse effects and disorders of angiotensin-converting enzyme inhibitor drugs treatment in patients with various cardiac diseases who prescribed those treatments. It also evaluates the risk of angiotensin-converting enzyme inhibitor drugs on long term therapy of patients. Subjects and methods: this cross-sectional study was carried out in Al Hussein-teaching hospital at Al Nasiriya city, south of Iraq. The research started at November 2016 until April 2017. Eighty one patients (52) males and (29) females], age (34-77 years) were enrolled in this study. All of the patients were diagnosed with cardiac diseases by specialist doctors and currently on angiotensin-converting enzyme inhibitor drugs for long term therapy. The data collected from patients through a questionnaire list designed and developed for this study. The list concerned with the disorders and drugs-related data in addition to the patients' general data. The collected results were analyzed in order to construct tables, figures and other necessary research requirements. Results and conclusions: in this study, most of the cases are treated with angiotensin-converting enzyme inhibitor drugs for hypertension (97.5%), and captopril represents the most popular of them (52 %). The most common significant results among the disorders associated with angiotensin-converting enzyme inhibitor treatment in patients were osteoporotic back pain (79 %), osteoarthritic joint pain (87.65 %), and gastrointestinal disorders like constipation, abdominal pain and chest pain were (66.7%), (53%), and (56.8%) respectively.

Keywords: *Bone, Joint, Inflammatory Bowel Disorders, Angiotensin.*

Introduction

Overview

In recent years, stressful and fiercely competitive lifestyles and food habits have compounded the problems of hypertension. Long-standing and stressful, progressively rising hypertension can lead to many disorders, including myocardial infarction, cerebrovascular events, congestive heart failure, peripheral arterial insufficiency, premature mortality [1]and renal dysfunction leading to glomerulosclerosis and kidney artery aneurysm [2].

Angiotensin Converting Enzyme Inhibitors

A number of therapies are available, but (ACE) inhibitors have been the preferred first-line therapy for hypertension, congestive heart failure, left ventricular (LV) systolic dysfunction and MI [3, 4]. (ACEIs) have been in use for the past two decades, and the interest in them is still growing. Recently, the discovery of domain-selective ACEIs and new members of the (RAS) (that is, angiotensin-converting enzyme 2) have again fueled the interest of researchers. Some new studies have expanded the already impressive clinical profile of ACE is. This review traces some already known and new facets of ACE inhibition and introduces new advances in the designing of a new generation of ACE is, number of ACE is currently in the market.

The ACE is differ in the chemical structure of their active moieties, as well as in their potency, bioavailability, plasma half-life, route of elimination, distribution and affinity for tissue-bound ACE, and whether they are administered as prodrugs. The ACE is may be classified into three groups according to the chemical structure of their active moiety. Captopril is the prototype of the sulfhydryl-containing ACEis; others are fentiapril, pivalopril, zofenopril and alacepril. Fosinopril

is the only ACE inhibitor containing a phosphinyl group as its reactive moiety. The majority of other ACE is, like lisinopril, enalapril and perindopril, contain a carboxyl moiety [5].

Recent Indications of Aceis

The first ACE inhibitor, captopril was approved by the FDA in 1981. Ten ACE inhibitors are currently available in the U.S. for treating hypertension, and all are available as generic drugs: benazeprilcaptopril, enalapril ,fosinopril , lisinopril, moexipril, Perindopril, quinapril, ramipril, and trandolapril [6].In addition, most ACE inhibitors are approved to treat heart failure (captopril, enalapril, fosinopril, lisinopril, quinapril, ramipril, and trandolapril), and some are used to prevent nephropathy.[7]

Mechanism of Action of Aceis

They interfere with the renin-angiotensin system by inhibiting the enzyme responsible for the conversion of angiotensin I to angiotensin II. However, the effect of these drugs may not be entirely explained by their actions on the renin-angiotensin system. Because the ACE is identical to kininase II, ACE inhibition not only interfere with the formation of angiotensin II but also enhances the action of kinins and substance P which may be more important than angiotensin suppression in mediating the effects of ACE inhibitors.

Hemodynamic and prognostic benefits of ACE inhibitors may be attenuated by the co administration of aspirin, which blocks kinin-mediated prostaglandin synthesis. Pulmonary adverse effects of these drugs seems to be related to their effect on kinin system and substance P.[8-9]

Other Effects

In Addition to treatment of hypertension, congestive heart failure, MI, LV systolic dysfunction, there are other uses of ACEI:

Memory-Enhancing Effect

In 2002, Amenta *et al* [10].Reviewed the majority of controlled clinical trials and observed that ACEi treatment (including perindopril, captopril and 397isinopril) positively influenced cognitive function independently of its BP-lowering effects, and patients treated with ACEi displayed better results than those on diuretics and ß-blockers. Long-term administration of the ACE inhibitor captopril (400 mg/l through the drinking water), either from the time of weaning or from the age of 6 months (that is, several months after hypertension was established), improved performance in working memory spatial task in both spontaneously hypertensive rats and WKY at 24 months of age [11].

Antioxidant Effects

In addition to reducing levels of Ang II and increasing bradykinin, ACEis have important implications for vascular oxidative stress. All major cell types of the vascular wall (endothelium, smooth muscle and fibroblasts) contain the enzyme NADPH oxidase, which is responsible for the production of superoxide anion, [12] which is activated in response to Ang II [13] and leads to both hypertension [14] and smooth-muscle cell hypertrophy. [15]

Plaque Stabilization

Angiotensin II stimulates endothelin release. Endothelin is one of the most potent coronary vasoconstrictors, and its local release might, in the presence of a susceptible atherosclerotic lesion, accelerate plaque rupture. [16،17] Hypomagnesemia has also been shown to cause an increase in coronary vascular reactivity and could potentially accelerate plaque rupture [18, 19] Ang II can trigger most of the changes reported to be associated with magnesium deficiency, including induction of pro-oxidant and proinflammatory conditions [20].

Adverse Effects

Like all antihypertensive agents, ACEIs can cause hypotension particularly in patients with elevated plasma renin activity. Therefore, lower starting doses should be used under these conditions [21]. ACEIs can cause hyperkalemia because of a decrease in aldosterone [22]. Especially in patients with impaired kidney function or in patients who are taking potassium supplements (including salt substitutes) or potassium-sparing diuretics [23, 24].

ACEIs can cause a reversible decline in renal function in the setting of decreased renal perfusion due to bilateral renal artery stenosis,[25]severe congestive heart failure [26] or volume depletion [27].

Coughing is a frequent side effect of ACEIs. The mechanism is not known but may involve increased levels of bradykinin or substance P and stimulation of vagal C fibers [28].

Thromboxane antagonism, aspirin and iron supplementation reduce coughing induced by ACEIs [20]. Angioedema, a rare but potentially life-threatening side effect of ACEIs, is characterized by localized swelling of the lips, tongue, mouth, throat, nose or other parts of the face. The mechanism seems to involve bradykinin or one of its metabolites [28].

If administered in the second or third trimester of pregnancy, ACEIs can cause oligohydramnios, fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria, neonatal renal failure, hypotension and death. These effects result from blockade of the conversion of Ang I to Ang II in the developing fetal kidneys leading to fetal hypotension [29] for this reason, ACEIs should be stopped once a pregnancy has been confirmed.

Materials and Methods

Demographic Characteristics

This cross-sectional study was carried out in Al Hussein-teaching hospital at Al Nasiriya city, south of Iraq. The research started at November 2016 until April 2017. During this time, 81 patients were enrolled in the study, males (65.20%) and females (34.80%). The patients were diagnosed and treated with ACEi drugs by specialist physicians. They were at various ages, the age range was (34-77) years, and different occupations and economic states; employees (40.70 %), Retired (38.30 %), Students (0%) and Housewives (21 %). The social states of patients were varied also, single (2.50 %) and married (97.50 %), with various living areas Urban (93.80 %) and Rural (6.20 %).

The race or ethnic group characteristics of males and females that involved in this study were white (95 %) and black (5 %). The study was based on individual using ACE inhibitor drugs with duration of treatment between (8-130 months). The body mass index (BMI) range was (21-48 Kg/m^2).

Inclusion and Exclusion Criteria

The patients who were diagnosed with hypertension, myocardial infarction, heart failure and other cardiovascular diseases and were treated with different ACE is like captopril, enalapril, lisinopril and others, all were included in this study. The patients who had other interfering diseases like inflammatory bone and joint disorders or inflammatory bowel diseases were excluded from the study. Patients on medications and/or supplements that may affect on the study data were also excluded from the sample of the study.

Questionaire List

The following demographic and drug-related data were questioned and collected properly for all of the patients who were involved in the study population.

Table 1: Patients details

No.	Category	Results
1	**Name of patient**	
2	**Gender**	
3	**Age**	
4	**Race**	
5	**Social state**	
6	**Economic state**	
7	**Occupation**	
8	**Drug history (ACEi):** **Dose:** **Duration of treatment:**	
9	**Disease history**	
10	**Diagnosis**	
11	**Body weight (Kg)**	
12	**Body height (cm)**	
13	**Body mass index (BMI) Kg/cm^2**	

Signs and Symptoms of Osteoporosis, Osteoarthritis, and Inflammatory Bowel Diseases

Osteoporosis

Back pain, Stooped posture, Bone fracture

Loss of height, X-ray, U/S, BMI.

Osteoarthritis

Joint pain, Tenderness, Stiffness, Loss of flexibility, Grating sensation, Bone spurs.

Irritable Bowel Syndrome

Abdominal pain or cramps, Bloating, Flatulence or gases, Diarrhea, Constipation, Mucous in stool.

Colitis

Abdominal pain, Diarrhea, Hemorrhoid ,Fever, Chills, Inflammation.

Peptic Ulcer Disease

Burning abdominal pain, Change in appetite, Vomiting, Indigestion, Chest pain, Weight loss , Bloody or dark stool .

Statistical Analysis

The collected data in this study were expressed as percentages (%) and then analyzed for their significance by using *chi square* analysis test. The results were then arranged in tables and figures for convenience.

Results

Demographic Data

Table 2: Demographic data of the study population

NO.	Category	Sub-category	Frequency	Percentage
1	Age (year)		34 - 77 Years	---
2	Gender	Male	52	**64.2** % [a]
		Female	29	35.80%
3	Occupation	Employee	33	**40.7** % [a]
		Retired	31	38.30%
		Student	0	0 %
		Housewife	17	21 %
4	Social state	Single	2	2.5 %
		Married	79	**97.5** % [b]
5	Economic state	Good	21	25.9 %
		Middle	29	35.8 %
		Bad	31	**38.27 %** [a]
6	Race	White	77	**95** % [b]
		Black	4	5 %
7	Living region	Urban	76	**93.8** % [b]
		Rural	5	6.2 %
8	Body Mass Index (BMI) Kg/m²		21- 48	---

Data were expressed as percentages (%) and averages.
Represents significant value (P<0.05) as compared to other values
Represents a significant value (P<0.001) as compared to other values

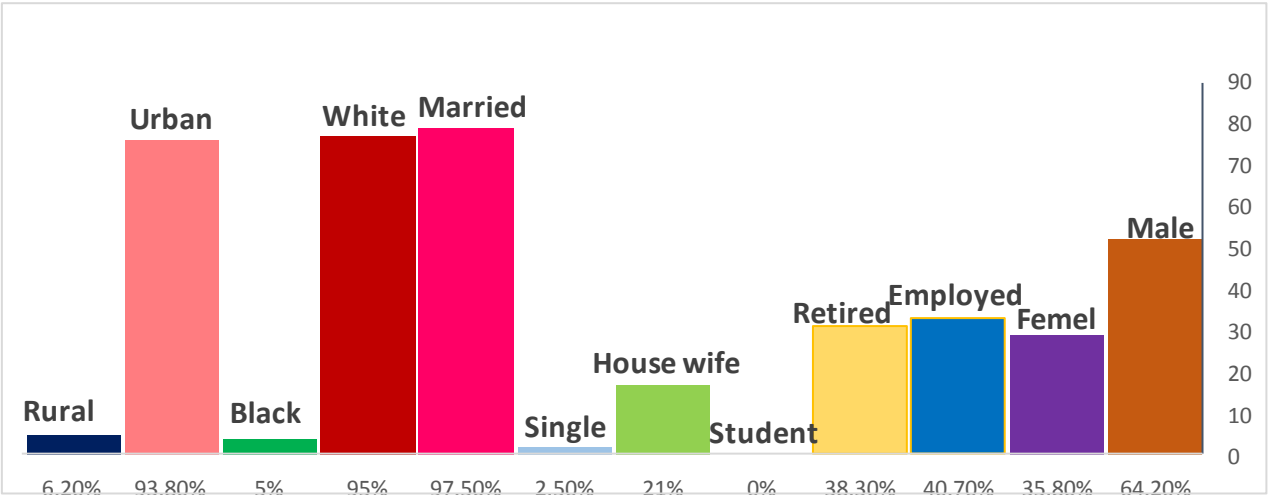

Figure 1: The demographic criteria of the study population

Patients Using ACEi Medications

Table 3: Frequency of ACE inhibitor drugs used by patients in the study

NO	ACEi Drug	Frequency	Percentage %
1	Lisinopril	30	37 %
2	Enalapril	9	11 %
3	Captopril	42	**52** %[a]

Data are expressed as percentages %
Represents a significant value (P<0.05) as compared to other values

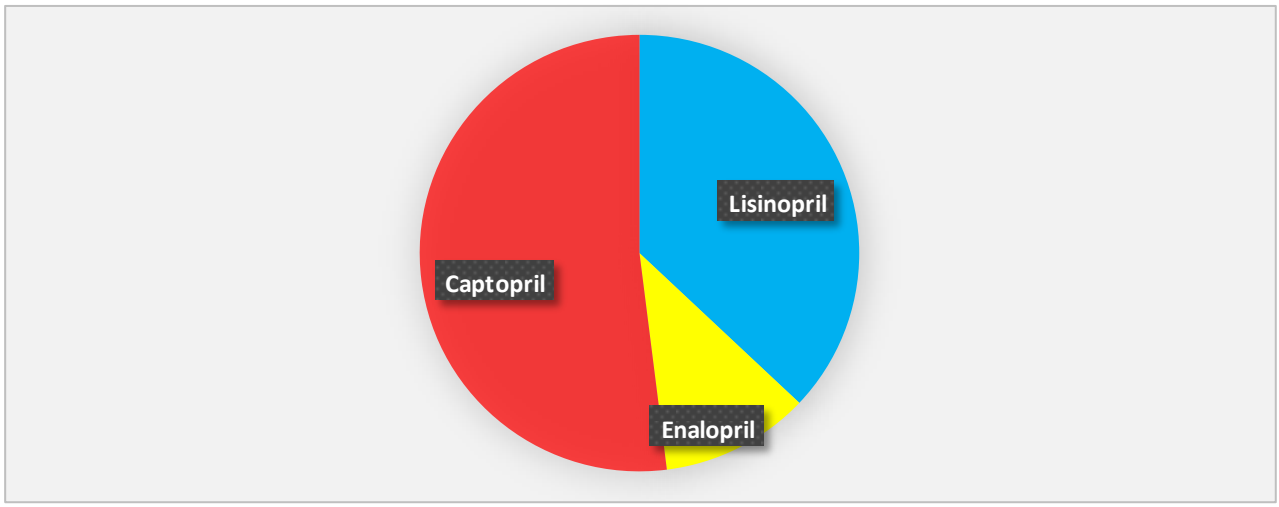

Figure 2: The percentages of ACEi drugs used by patients in the study

Disease Characteristics of Patients

Table 4: Disease characteristics of patients included in the study population

NO.	Criterion	Sub criterion	Frequency	Percentage
1	Disease history	Hypertension	79	**97.5** % [b]
		Heart failure	2	2.5 %
		Angina	7	8.6 %
2	Associated diseases	Diabetes mellitus	25	**30.8** % [b]
		Renal failure	4	5%
		Asthma	2	2.50%
		Hypercholesterolemia	1	1.20%
		Migraine headache	1	1.20%
		Tachycardia	1	1.20%
3	Non-associated diseases	Other non-related disorders e.g. infections	41	**50.6** % [a]

Data were expressed as percentages (%) and averages
Represents significant value (P<0.05) as compared to other values
Represents a significant value (P<0.001) as compared to other values

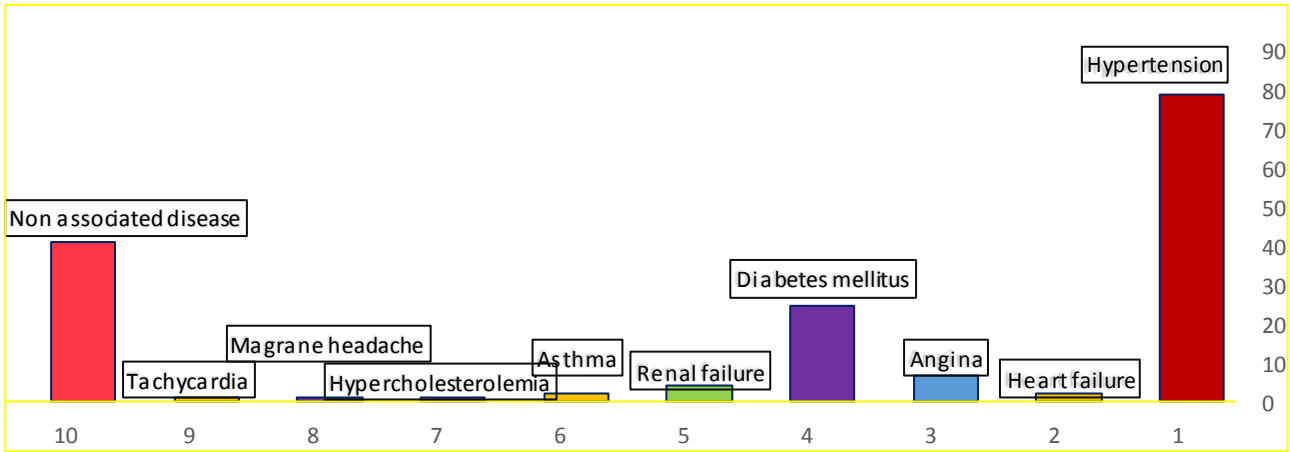

Figure 3: Disease characteristics of patients in the study population

Doses and Duration of Treatment by ACEi Drugs

Table 5: Doses and duration of treatment by ACEi drugs and used by the patients in the study population

No.	Drug	Dose	Duration	Frequency	Percentage
1	Lisinopril	2.5 mg	6 months	1	1.2 %
		5 mg	3 -24 months	6	7.5 %
		10 mg	9 - 36 months	7	**8.65** % [a]
		20 mg	3 - 120 months	16	19.75%
2	Captopril	5 mg	180 months	1	1.2 %
		25 mg	8 -120 months	28	**34.5** % [a]
		50 mg	8 - 130 months	13	16 %
3	Enalapril	10 mg	2 months	1	1.2 %
		20 mg	3 - 120 months	8	**10** % [a]

Data are expressed as percentages %
a represents a significant value (P<0.05) as compared to other values

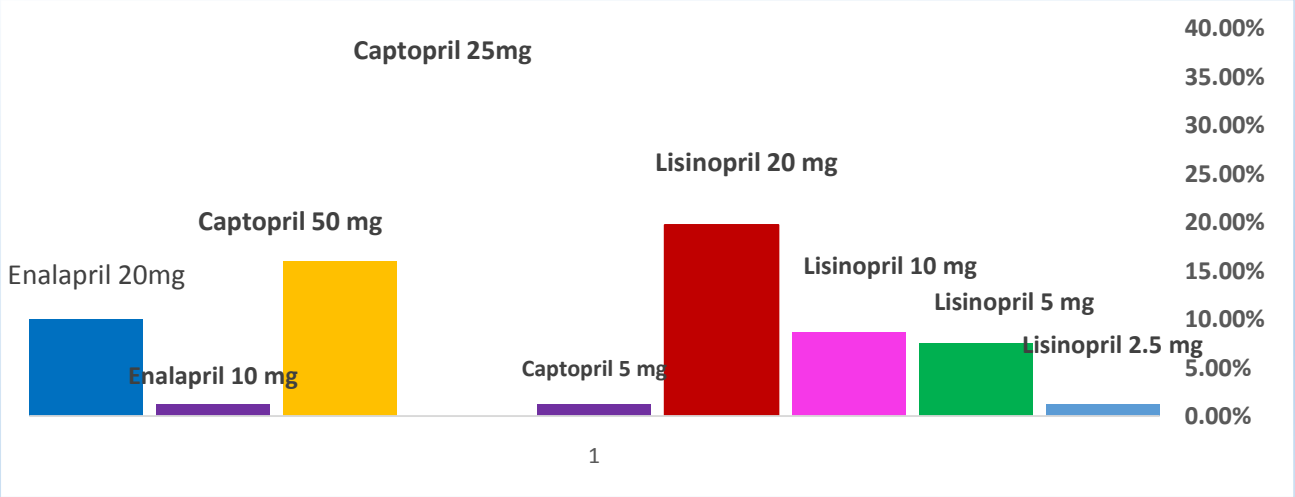

Figure 4: Doses and duration of treatment by ACEi drugs and used by the patients in the study population

Signs and Symptoms of Bone, Joint and Bowel Disorders in ACEis-treated Patients

Table 6: Signs and Symptoms of Bone, Joint and Bowel Disorders in ACEis-treated Patients included in the study population

NO	Disease	Symptoms	Frequency	Percentage
1	Osteoporosis	Back pain	64	**79** % [a]
		Stooped posture	32	39.5 %
		Bone fracture	13	16 %
		Loss of height	17	21 %
2	Osteoarthritis	Joint pain	71	**87.65** % [a]
		Tenderness	28	34.5 %
		Stiffness	36	44.5 %
		Loss of flexibility	47	**58** % [a]
		Grating sensation	23	28.4 %
		Bone spurs	18	22 %
3	Irritable Bowel Syndrome	Abdominal pain	41	50.6 %
		Bloating	52	64 %
		Gas	52	64 %
		Diarrhea	7	8.6 %
		Constipation	54	**66.7** % [a]
4	Colitis	Abdominal pain	43	**53** % [a]
		Diarrhea	5	6 %
		Fever	38	**47** % [a]
		Chills	17	21 %
		Hemorrhoids	17	21 %
4	Peptic Ulcer Disease	Burning or abdominal pain	51	**63** % [a]
		Vomiting	17	21 %
		Appetite change	26	32 %

		chest pain	46	**56.8** % [a]
		Unexplained weight loss	13	16 %
		Dark stool	4	5 %
		Indigestion or dyspepsia	21	26%

Data are expressed as percentages %
a represents a significant value (P<0.05) as compared to other values

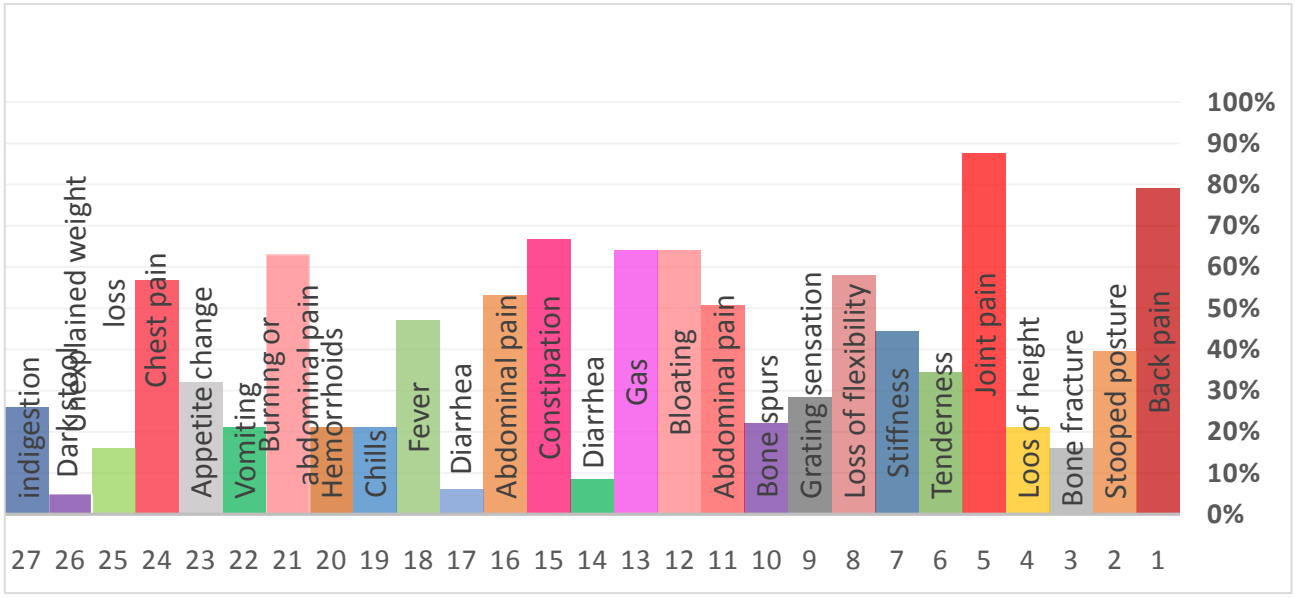

Figure 5: Signs and Symptoms of Bone, Joint and Bowel Disorders in ACEis-treated Patients included in the study population

Discussion

In this study, a significantly higher number of disorders were observed associated with long-term use of ACE inhibitor drugs especially in elderly patients (table 3-5). The ACE inhibitors produce vasodilation by inhibiting the formation of angiotensin II. They also break down bradykinin (a vasodilator substance). Therefore, ACE inhibitors, by blocking the breakdown of bradykinin, increase bradykinin levels, which can contribute to the vasodilator action of them. The increase in bradykinin is also believed to be responsible for troublesome side effects of ACE inhibitors.

Moreover studies have focused on the pharmacological characteristics of the first nonpeptide bradykinin receptor agonist 8- [2, 6-dichloro-3 - [N] - [(E) - 4 - (N-methylcarbamoyl) cinnamidoacetyl-N-methylamino] benzyloxy]- 2- methyl -4 - (2-pyridylmethoxy) quinoline (FR190997).

FR190997, whose structure is quite different from the natural peptide ligand, but is similar to the nonpeptide antagonists FR165649, FR167344 and FR173 657, potently and selectively interacts with the human B_2 receptor and markedly stimulates inositol phosphate formation in transfected Chinese hamster ovary (CHO) cells.

FR190997 induces concentration-dependent contraction of isolated guinea pig ileum. In vivo, FR190997 mimics the biological action of bradykinin and induces hypotensive responses in rats with prolonged duration, presumably as a consequence of its resistance to proteolytic degradation.

Therefore, FR190997 is a highly potent and subtype-selective nonpeptide agonist, which displays high intrinsic activity at the bradykinin B_2 receptor [22]. Moreover, while BK acts as a full agonist in man, rabbit and pig, FR 190997 behaves as a full agonist on human, as partial agonist on rabbit, and as pure antagonist on pigB_2 receptors [23].

Osteoporotic Effect

Experimental evidence suggests that angiotensin II promotes bone loss by its effects on osteoblasts. It is therefore plausible that ACE inhibitor may reduce rates of bone loss. The objective of this study is to examine the independent effects of ACE inhibitor on bone loss in older patients and those that taken the ACE inhibitor drugs for long periods of time. The continuous use of ACE inhibitors was associated with a small but significant increase in the average rate of BMD loss (table 3-5) at total hip and trochanter over 4 years after adjustment for confounders [30].

Back Pain

The ACE inhibitor drugs increase the free bradykinin present in the blood and various other soft tissues. The main function of bradykinin is to increase the sensation of pain. Bradykinin also sensitizes free nerve endings, making them hypersensitive to heat and light touch and creating an overall sensation of soreness. A secondary function of bradykinin is to promote the production of histamine. It does this by binding to most cells in the affected area and induces them to release histamine [31].

It also does this indirectly through the amplification of the pain process mentioned above. There are nerve centers in the brain and spinal cord which respond to the amplified pain impulses by sending efferent impulses to the appropriate nerve endings housed in the involved soft tissues. These nerve endings being bombarded by efferent impulses then release substance P, which also binds to most cells and further boosts histamine production [31]. Further release of bradykinin precursors cause additional bradykinin to be formulated.

This added bradykinin binds itself to the membranes of nearby cells and ultimately causes the release of polyunsaturated fatty acids (PUFAs) from the membranes. These PUFAs cause the production of prostaglandins. These prostaglandins cause vasodilation in the surrounding tissues and increased capillary permeability.

The prostaglandins also bind themselves to receptor sites on involved free pain nerve endings and promote additional pain impulses and bradykinin release. This is important because enzymes in the blood continually work to deactivate bradykinin, and this process keeps bradykinin release going until the source of irritation has been removed.

Osteoporotic Fracture

The contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture is poorly understood. Hypertension and osteoporosis are two major public health burdens of the general population, which share many of the same risk factors such as advance age, early menopause, smoking and physical inactivity. Many experimental studies suggested that there is a biological link between hypertension, anti-hypertension medications and bone [32, 36]. However, existing human evidence on the contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture is either scarce or conflicting [38, 44]. Given the high prevalence of hypertension and osteoporosis in the elderly population, understanding the contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture will substantially improve general health of humans.

Bone Spur

Hypertension and bone mineral density (BMD) have a major pathophysiologic link between blood pressure regulation and calcium metabolism. High blood pressure is associated with abnormalities of calcium metabolism, which induces increased calcium leak from bone [32-34]. The calcium leak from bone will be eventually excreted by kidney in the form of urine [33]. In support, hypertension has been shown to be associated with hypercalciuria and hypercalciuria is related to decrease BMD [42, 48].

Loss of Height

Hypertension-bone relationship is related to parathyroid hormone (PTH) [35]. It has been shown that the circulating level of PTH is positively correlated with blood pressure [46, 49]. The elevated PTH due to hypertension leads to an increased bone resorption, decreased bone mass and bone quality [35]. Finally, the oxidative stress pathway may be involved in the hypertension-bone relationship, because oxidative stress is well correlated with hypertension [43-47].

High level of oxidative stress due to excessive reactive oxygen species increases bone loss by inhibiting bone formation and promoting bone resorption [37, 39]. Those abnormalities related to hypertension may eventually be responsible for increased bone loss and low BMD [40, 45]. The findings were unable to be replicated in an U.S. study, in which the use of ACE inhibitors marginally increased bone loss in older men [41].

Osteoarthritis (OA)

It is now accepted that the excessive and spontaneous inflammation plays a significant role in the molecular pathogenesis of OA,

table 3-5, figure 3-5 in the study, contributing to a highly catabolic state, chondrocyte apoptosis, and the resultant progressive degeneration of articular cartilage [50–51]. Bradykinins, a family of oligopeptides derived from the enzymatic action of kallikreins on kininogens, can promote all the major signs of inflammation, including hyperemia, leakage of plasma proteins, and pain [52–53].

The presence of BK was previously reported in the synovial fluid from patients affected by arthritis of different etiologies, including OA [54, 55]. B_2-bradykinin receptor (BDKRB2) mediates most of the inflammatory actions of bradykinin [56]. B_2-bradykinin receptor is widely present in most tissues, including joint tissues. BDKRB2 has been detected on the synovial lining cells, fibroblasts, and endothelial lining cells of blood vessels from OA patients [54, 57]. Clinically, the administration of B_2 receptor antagonists effectively reduced the inflammatory articular pain and knee OA progression, suggesting the BDKRB2 is involved in the development of OA [54, 58].

The genetic variants of BDKRB2 may lead to altered biological activities of the functional protein. The gene polymorphisms of BDKRB2 have been shown to be related with ACEI-induced cough in hypertensive patients, left ventricular hypertrophy, and insulin resistance [59–60]. However, its relation with OA remains unknown. In this study, knee OA patients used to explore the role of BDKRB2 in OA.

Inflammatory Bowel Disorders

They are common disorder that affects the large intestine (colon). Table and figure 3-5 shown various disorders related to the chronic use of ACEis. Irritable bowel syndrome (IBS) commonly causes cramping, abdominal pain, bloating, gas, diarrhea and constipation. IBS is a chronic condition that you will need to manage long term; Bradykinin is a mediator of inflammation, responsible for pain, vasodilation, and capillary permeability. Bradykinin receptor 1 (B(1)R) and bradykinin receptor 2 (B(2)R) are G protein-coupled receptors that mediate kinin effects. The latter is constitutive and rapidly desensitized; the former is induced by inflammatory cytokines and resistant to desensitization.

The distribution of bradykinin receptors in human intestinal tissue was studied in patients with inflammatory bowel disease (IBD), namely ulcerative colitis (UC) and Crohn's disease (CD). Both B (2) R and B (1) R proteins are expressed in the epithelial cells of normal and IBD intestines. B (1) R protein is visualized in macrophages at the center of granulomas in CD. B (2) R protein is normally present in the apexes of enterocytes in the basal area and intracellularly in inflammatory tissue.

In contrast, B (1) R protein is found in the basal area of enterocytes in normal intestine but in the apical portion of enterocytes in inflamed tissue. B (1) R protein is significantly increased in both active UC and CD intestines compared with controls. In patients with active UC, B (1) R mRNA is significantly higher than B(2)R mRNA. However, in inactive UC patients, the B (1) R and B (2) R mRNA did not differ significantly. Thus bradykinin receptors in IBD may reflect intestinal inflammation. Increased B(1)R gene and protein expression in active IBD provides a structural basis of the important role of bradykinin in chronic inflammation [60].

A much rarer complication and one that many physicians are not aware of is visceral angioedema, affecting primarily the small intestine but sometimes involving the stomach or colon. Patients typically present with abdominal pain and vomiting. The mechanism of this syndrome may involve increased levels of bradykinin, leading to increased vascular permeability in the viscera. One other potential cause of abdominal pain in patients treated with ACE inhibitors is drug-induced pancreatitis.

Conclusions

The ACE inhibitor therapy is now a mainstay of clinical practice. The ease with which these compounds can be used in most subjects is reassuring; however, numerous considerations arise when these drugs are used in certain patient types, including the elderly and/or volume contracted patient and/or those with comorbid conditions of a renal or cardiac nature. Another explanation for the cause of monitor the patients that have a greater rise in serum creatinine if they are taking an ACE inhibitor may relate

to the known effects of ACE inhibitors on the sympathetic and parasympathetic nervous systems.

In this study, Tables 3-1, 3-2, and 3-4, found the long use of an ACE inhibitor drugs among several of age groups lead to a wide range of adverse effects of osteoporotic effects.

The antihypertensive ACE inhibitors drugs impact osteoporosis directly and indirectly by affecting bone metabolism, strength and density [32]. Also ACE inhibitors drug have effect on osteoarthritis by induce joint pain, loss of flexibility, tenderness and other of osteoarthritis adverse effect, because the ACE inhibitors drugs increase the free bradykinin present in the blood and various other soft tissues. This increase the sensation of pain.

Bradykinin also sensitizes free nerve endings [31]. Other adverse effect of ACE inhibitors drugs on irritable bowel syndrome also arise in various percentages, so, a much rarer complication and one that many physicians are not aware of is visceral angioedema, affecting primarily the small intestine but sometimes involving the stomach or colon. Patients typically present with abdominal pain and vomiting. After wide use of captopril, enalapril and 405isinopril, and investigational trials of nearly a dozen newer agents, a sufficiency of clinical observation, experimental evidence and accurate post marketing recording of events is accumulating to allow insight into the major toxicities with regard to more intelligent patient selection, more rational dosing and proper identification of risk factors. The most common adverse reactions are removed.

Recommendations

- A large sample of patients is recommended for future work to correlate and authenticate the results of this study.
- Another ACEi-related disorder may be involved in future studies.
- The follow-up of ACEi-treated patients is quite important and should be performed by doctors and pharmacists.

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