THE RECENT DEVELOPMENTS ON ACE INHIBITORS- A REVIEW

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Summary

Hypertension is controlled by many hypothesis and pharmacological efforts. ACE inhibitor are found to be more effective and safe for secondary hypertension. ACE inhibitor have found to reduce the progress of Diabetic neuropathy. In the present review we have attempted to focus the medicinal importance of ACE inhibitors, their side effects and mechanism of action. The research of ACE inhibitors have inspired all the physicians, pharmacists as it will be the major route of treatment for hypertension.

Key-words: ACE inhibitor, Angiotensin,Hypertension, Proteinurea.

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Introduction

Hypertension is a chronic medical condition in which the blood pressure is elevated. It is shortened to HT, HTN or HPN. The word "hypertension", by itself, normally refers to systemic, arterial hypertension.[1]Hypertension can be classified as either essential (primary) or secondary. . It is common. About 90-95% of hypertension is essential hypertension.[2-5] Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours (adrenal adenoma or pheochromocytoma).

Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic renal failure.[6] At severely high pressures, defined as mean arterial pressures 50% or more above average, a person can expect to live no more than a few years unless appropriately treated.[7]

History [8-11]

Sr. No.	Year	Description
1.	1956	Leonard T. Skeggs and his colleagues discovers angiotensin converting enzyme (ACE) in plasma
2.	1965	Brazilian scientist Sergio Ferreira reported a 'bradykinin potentiating factor (BPFs) present in the venom of bothrops jararaca, a South American pit viper. Dr SH Ferreira then proceeded to John Vanes laboratory as a Post-Doc with his already isolated BPFs. The conversion of the inactive angiotensin I to the potent angiotensin II was thought to take place in the plasma.
3.	1967	Kevin K. F. Ng and John R. Vane showed that the plasma (ACE) was too slow to account for the conversion of angiotensin I to angiotensin II *in vivo*.
4.	1975	David Cushman, Miguel Ondetti and Colleagues used peptide analogues to study the structure of ACE, using carboxypeptidase A as a model. Their discoveries led to the development of captopril, the first orally-active ACE inhibitor.
5.	1991	Japanese Scientists created the first ever milk-based ACE inhibitor in the form of a fermented milk drink, using specific cultures to liberate the IPP from the dairy protein.

Table .1 History

ACE inhibition

ACE inhibitors disrupt the RAAS by preventing the conversion of AT-I to AT-II. As a result, ACE inhibitors are used widely to treat hypertension. These agents reduce proteinuria and delay progression of renal disease in patients with diabetic nephropathy or nondiabetic kidney disease. Nevertheless, the use of ACE inhibitors has limitations. Some patients taking ACE inhibitors develop a reactive and persistent increase in ATII levels as a result of a compensatory stimulation of ACE independent pathways of production in tissues, a phenomenon known as AT II escape. These increased local levels of ATII may cause further target organ damage through effects at the AT, receptor. Inhibition of ACE, a nonspecific enzyme, also prevents the catabolism of other biologically active peptides, such as bradykinin, substance P, and prostaglandins. Although these vasodilators may augment the antihypertensive effect, they may also be responsible for some of the more troublesome side effects of ACE-inhibitor therapy-cough and angioedema. The cough associated with ACE-inhibitor use is sufficiently bothersome to lead to treatment discontinuation in -60% of patients who develop it.

Role of ACE in Renin - Angiotensin - Aldosterone system: [12-16]

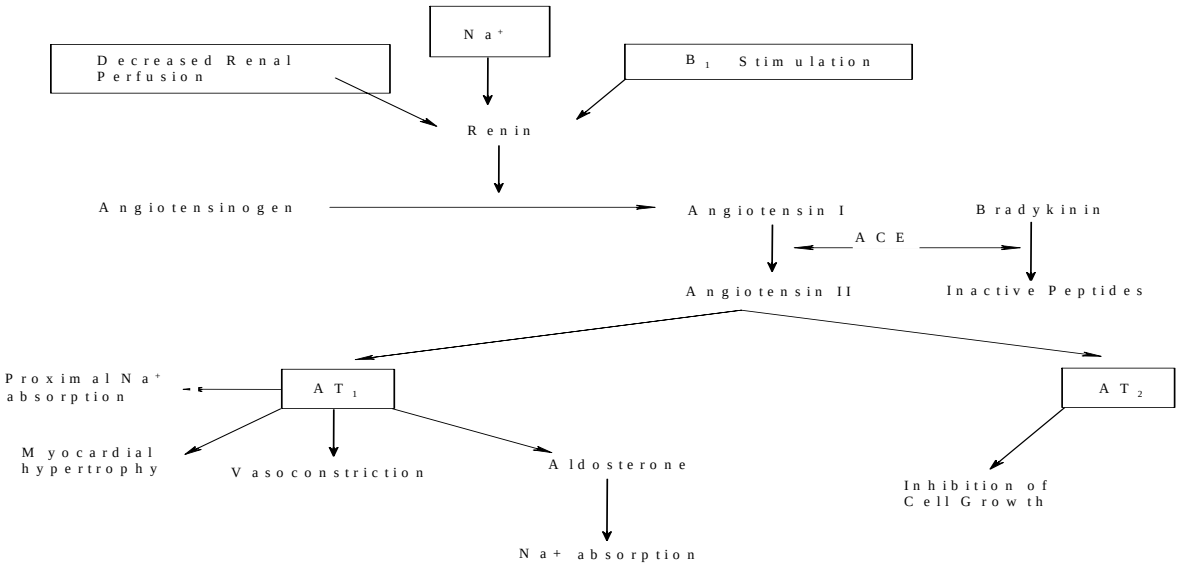


Figure 2: The Renin-Angiotensin-Aldosterone System.
ACE = Angiotensin converting enzyme
AT_1 and AT_2 angiotensin subtype I and II

Fig.1: Role of ACE in Renin - Angiotensin - Aldosterone system

Pharmacological effects of ACE inhibitors

With ACE inhibitor use, the effects of angiotensin II are prevented, leading to decreased blood pressure. The effects of angiotensin II are-vasoconstriction (narrowing of blood vessels), which may lead to increased blood pressure and hypertension -constriction of the efferent arterioles of the kidney, leading to increased perfusion pressure in the glomeruli. ventricular remodeling of the heart, which may lead to ventricular hypertrophy and CHF stimulation of the adrenal cortex to release aldosterone, a hormone that acts on kidney tubules to retain sodium and chloride ions and excrete potassium. Sodium is a "water-holding" molecule, so water is also retained, which leads to increased blood volume, hence an increase in blood pressure. Stimulation of the posterior pituitary to release vasopressin (also known as anti-diuretic hormone (ADH)) which also acts on the kidneys to increase water retention. Decrease renal protein kinase C.Epidemiological and clinical studies have shown that ACE inhibitors reduce the progress of diabetic nephropathy independently from their blood pressure-lowering effect. This action of ACE inhibitors is utilised in the prevention of diabetic renal failure.ACE inhibitors have been shown to be effective for indications other than hypertension even in patients with normal blood pressure. The use of a maximum dose of ACE inhibitors in such patients (including for prevention of diabetic nephropathy, congestive heart failure, prophylaxis of cardiovascular events) is justified because it improves clinical outcomes, independent of the blood pressure lowering effect of ACE inhibitors. Such therapy, of course, requires careful and gradual titration of the dose to prevent the effects of rapidly decreasing blood pressure (dizziness, fainting, etc.).

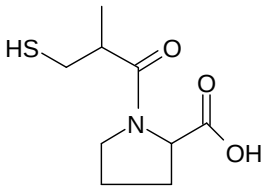
Adverse Effects of ACE inhibitors

Renal impairment	It is a significant adverse effect of all ACE inhibitors. Some suggest that it is associated with their effect on angiotensin II-mediated homeostatic functions such as renal blood flow. Renal blood flow may be affected by angiotensin II because it vasoconstricts the efferent arterioles of the glomeruli of the kidney, thereby increasing glomerular filtration rate (GFR). Hence, by reducing angiotensin II levels, ACE inhibitors may reduce GFR, a marker of renal function. Specifically, ACE inhibitors can induce or exacerbate renal impairment in patients with renal artery stenosis. This is especially a problem if the patient is also concomitantly taking an NSAID and a diuretic. When the three drugs are taken together, there is a very high risk of developing renal failure.[17]
Hyperkalemia	Suppression of angiotensin II leads to a decrease in aldosterone levels. Since aldosterone is responsible for increasing the excretion of potassium, ACE inhibitors ultimately cause retention of potassium.
Angioedema	Due to increased bradykinin levels. There appears to be a genetic predisposition towards this adverse effect in patients who degrade bradykinin more slowly than average.[18]
congenital malformations, stillbirths, and neonatal deaths	ACE inhibitors taken during the first trimester have been reported to cause it.
hypotension, renal dysplasia, anuria/oliguria, oligohydramnios, intrauterine growth retardation, pulmonary hypoplasia, patent ductus arteriosus, and incomplete ossification of the skull.	These are the commonly reported fetal abnormalities.

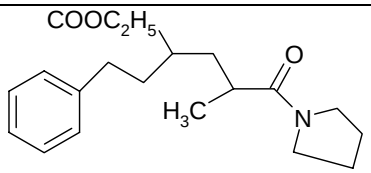
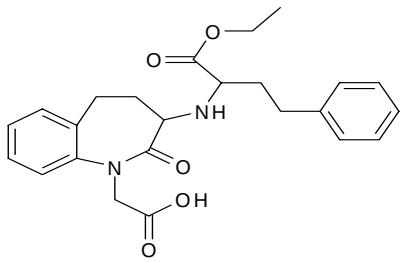
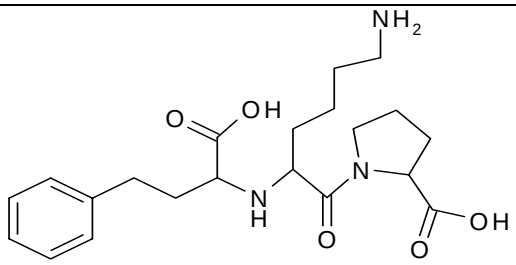
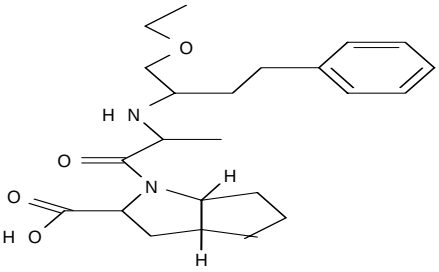
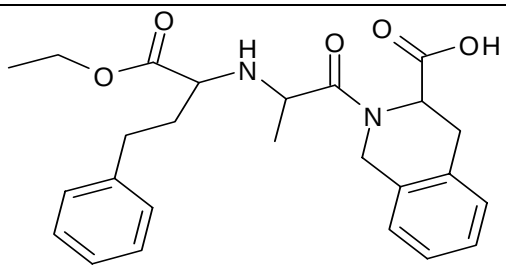
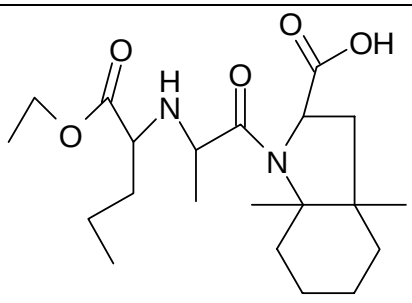
Table 2 ;Adverse Effects of ACE inhibitors

ACE inhibitors can be divided into three groups based on their molecular structure:

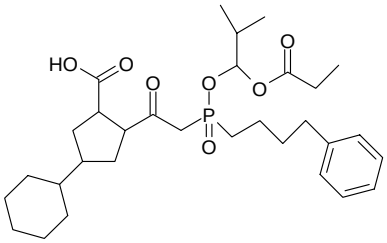
A) Sulfhydryl-containing agents

Captopril	

B) Dicarboxylate-containing agents

Enalapril	
Benazepril	
Lisinopril	
Ramipril	
Quinapril	
Perindopril	

C) Phosphonate-containing agents

Fosinopril	

ACEI equivalents

The ACE inhibitors have different strengths with different starting dosages. Dosage should be adjusted according to the clinical response. [19-21]

ACE inhibitors dosages for hypertension				
		Dosage		
Name	**Equivalent daily dose**	**Start**	**Usual**	**Maximum**
Benazepril	10 mg	10 mg	20–40 mg	80 mg
Captopril	50 mg (25 mg bid)	12.5–25 mg bid-tid	25–50 mg bid-tid	450 mg/d
Enalapril	5 mg	5 mg	10–40 mg	40 mg
Fosinopril	10 mg	10 mg	20–40 mg	80 mg
Lisinopril	10 mg	10 mg	10–40 mg	80 mg
Moexipril	7.5 mg	7.5 mg	7.5–30 mg	30 mg
Perindopril	4 mg	4 mg	4–8 mg	16 mg
Quinapril	10 mg	10 mg	20–80 mg	80 mg
Ramipril	2.5 mg	2.5 mg	2.5–20 mg	20 mg
Trandolapril	2 mg	1 mg	2–4 mg	8 mg
Note: bid = 2 times a day, tid = 3 times a day, d = daily				

Table 3: ACEI equivalents

Contraindications and precautions [22-23]

The ACE inhibitors are contraindicated in patients with:

- Previous angioedema associated with ACE inhibitor therapy
- Renal artery stenosis (bilateral, or unilateral with a solitary functioning kidney)
- Hypersensitivity to ACE inhibitors
- ACE inhibitors should be used with caution in patients with:
- Impaired renal function
- Aortic valve stenosis or cardiac outflow obstruction
- Hypovolemia or dehydration
- Hemodialysis with high flux polyacrylonitrile membranes

ACE inhibitors are ADEC Pregnancy category D, and should be avoided in women who are likely to become pregnant.In the U.S., ACE inhibitors are required to be labelled with a "black box" warning concerning the risk of birth defects when taking during the second and third trimester. It has also been found that use of ACE inhibitors in the first trimester is also associated with a risk of major congenital malformations, particularly affecting the cardiovascular and central nervous systems.[24] Potassium supplementation should be used with caution and under medical supervision owing to the hyperkalemic effect of ACE inhibitors.

Conclusions

Secondary hypertension and it's management has become challenging. ACE inhibitors have created interest amongst the physician and pharmacists. Though ACE was discovered in 1956, a very little research work has been carried out. In 1975 Captopril the first orally active ACE inhibitor was developed. Now medicinal chemist have designed various inhibitors based on molecular structure and chemical entity attached. This has led to discover many more ACE inhibitors with promising absorption, lipophilic characters and other physico-chemical properties. There is a better scope for the search of these ACE inhibitors.

References

1. Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright. Human Biology and Health. Englewood Cliffs, New Jersey, USA: Prentice Hall.1963.
2. Carretero OA, Oparil S. "Essential hypertension. Part I: definition and etiology". Circulation 101 (3),2000,: 329–35.
3. Oparil S, Zaman MA, Calhoun DA. "Pathogenesis of hypertension". Ann. Intern. Med. 139 (9),2003: 761–76.
4. Hall, John E.; Guyton, Arthur C.. Textbook of medical physiology. St. Louis, Mo: Elsevier Saunders, 2006, 228.
5. Hypertension:eMedicine Nephrology" ,241381,An overview.
6. Pierdomenico SD, Di Nicola M, Esposito AL, et al.. "Prognostic Value of Different Indices of Blood Pressure Variability in Hypertensive Patients". American Journal of Hypertension 22 (8):2009,842–7.
7. Guyton and Hall. Textbook of Medical Physiology (7th ed.). Elsevier-Saunders. ,2005,220.
8. Ng, K. K. F. "Conversion of Angiotensin I to Angiotensin II". Nature 216,1967, (5117): 762.
9. Ng, K. K. F. "Fate of Angiotensin I in the Circulation". Nature 218 ,1968, (5137): 144.
10. Ng, K. K. F.. "Some Properties of Angiotensin Converting Enzyme in the Lung in vivo". Nature 225,1970,: 1142.

11. Hata. "A placebo-controlled study of the effect of sour milk on blood pressure in hypertensive subjects.". The American journal of clinical nutrition 64 (5),1996: 767–71.
12. M. Kanitkar, “Renovascular Hypertension: Review Article”. Indian Pediatrics. 2005; 42: 47-54
13. Theodore L GoodFriend, “Angiotensin receptors and their antagonists”. Drug Therapy; 1996, 334, 1649-54
14. Julie A. Brousil, John M. Burke, “Olmesartan Medoxomil: An Angiotensin II-Receptor Blocker” Clin Ther. 2003;25: 1041-55
15. David H.G. Smith, “Treatment of Hypertension with an Angiotensin II-Receptor Antagonist Compared with an Angiotensin-Converting Enzyme Inhibitor: A Review of Clinical Studies of Telmisartan and Enalapril.” Clin Ther. 2002; 24:1484-1501
16. Ursula C. Brewster, Mark A. Perazella, “The Renin-Angiotensin-Aldosterone System and the Kidney: Effects on Kidney Disease”. Am J Med. 2004; 116: 263–72.
17. Hoogwerf (2000). "The HOPE study. Ramipril lowered cardiovascular risk, but vitamin E did not". Cleveland Clinic journal of medicine 67 (4): 287–93.
18. Thomas (2000). "Diuretics, ACE inhibitors and NSAIDs--the triple whammy.". The Medical journal of Australia 172 (4): 184–5. PMID 10772593.
19. Molinaro (2002). "Angiotensin-converting enzyme inhibitor-associated angioedema is characterized by a slower degradation of des-arginine(9)-bradykinin.". The Journal of pharmacology and experimental therapeutics 303 (1): 232–7.
20. What are the dose comparisons of all ACE inhibitors used in hypertension? TripAnswers TRIP Database, May 25, 2007. Accessed 2009-11-21 .
21. Common Medication Conversions (Equivalents): Ace Inhibitors. GlobalRPh.com. Accessed 2009-11-22.
22. Treating High Blood Pressure and Heart Disease: the ACE Inhibitors. Consumer Reports Health Best Buy Drugs. 2009.
23. Rossi S, editor. Australian Medicines Handbook 2006. Adelaide: Australian Medicines Handbook; 2006.
24. Cooper. "Major congenital malformations after first-trimester exposure to ACE inhibitors.". The New England journal of medicine 354 (23),2006: 2443–51.