Original Article

Effect of Captopril and Imidapril on Tracheal Tissue

Comparison between Captopril and Imidapril in Relation to Their in Vitro Effects on Tracheal Tissue

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ABSTRACT

Objective: To observe two drugs (captopril and imidapril) action on smooth muscle tone of trachea and to facilitate safe and rational use of ACE inhibitors, particularly in patients with chronic obstructive airway disease.
Study Design: Comparative controlled in-vitro experimental Study.
Place and Duration of Study: This study was conducted at the Pharmacology Department, Army Medical College, Rawalpindi from December 2012 to May 2013.
Materials and Method: First the effect of bradykinin acetate on the smooth muscle of trachea has been observed. Cumulative concentration-effect relationship was studied with different concentrations of bradykinin on the smooth muscle starting with 22µg to 132 µg/dl. The method was done again with captopril 10^{-5} M concentration and imidapril 10^{-5}M respectively. In second set of experiments cumulative concentration-response curves were prepared by increasing concentrations of captopril and imidapril separately with fixed concentration of bradykinin 66 µg/dl.
Results: Dose related vacillating contraction of smooth muscle of trachea is produced by bradykinin. The average value of effect received with 132 µg/dl of bradykinin in the presence of captopril was 51.33 ± 2.79 and in the presence of imidapril was 25 ± 7.26. All these ACE inhibitors displaced the concentration effect curves of bradykinin to left and upward. On comparison among themselves it was observed that imidapril produced least enhancement of tracheal contraction. Similar results were produced by second set of experiments.
Conclusion: Imidapril is found to cause least enhancement of contraction caused by bradykinin on tracheal muscle. Further clinical trials may be conducted to establish the differential effects of various clinically used ACE inhibitors on the respiratory passages in hypertensive patients concomitantly suffering from COAD.
Key Words: ACE inhibitors, Adverse effects, Bradykinin, ACE, Guinea pig trachea, Oscillograph

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INTRODUCTION

Hypertension has multipart causes, affecting 972 million persons over the world[1]. It has been shown that by lowering blood pressure by drugs blood vessel damage is prevented and subsequently there is reduction in ailment and death rates. Various treatment options are available but among them Angiotensin-converting enzyme inhibitors (ACEI) has certain advantages. ACEI are useful for renal protection in hypertensive patients with diabetes. ACE is also called Kininase II and is Dipeptidyl Carboxypeptidase. ACE is an ectoenzyme and glycoprotein with a molecular weight of 170,000.[2] ACE enzyme inactivate bradykinin. in addition to transforming Angiotensin I to II.

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Captopril and enalapril, heightens the bronchial contraction and microvascular leakage caused by bradykinin.[3],[4], indicating a process of ACE inhibitor-related cough. In guinea pigs, long term intake of captopril causes impulsive coughing, which is antagonised by icatibant (bradykinin antagonist)[5] Bradykinin produces broncho constriction either directly or indirectly by releasing mediators such as prostaglandins and tachykinins.

This fact has been now proved in many aspects that all ACE Inhibitors are not tantamount [6} their chemical structure is different .[7] It has been seen that ACE inhibitors are responsible for production of cough and wheeze as their adverse effects. The exact mechanism of production of these adverse effects is not clear. This point is well known that this effect is due to inhibition of metabolism of bradykinin, which leads to its accumulation in airways. Bradykinin causes cough by irritation of vagal C-fibers in bronchial walls.

. Findings of one large scale study suggest that few individuals can suffer from dyspnea and wheezing but no causative relationship was sorted out.

In this study we aim to compare the effects of Imidapril and Captopril on tracheal muscle contraction induced by bradykinin in vitro.

MATERIALS AND METHODS

Bradykinin acetate and Phentolamine Hydrochloride from Sigma Chemical Co, USA. Captoril Disulfide and Imidapril Hydrochloride was kindly provided by Chemo S.A.Lugano Brach, Hetero Drug Limited and Tanabe/Seiyaku Japan respectively. Indomethacin Acetate by Shanghai-Chang-Hua industry limited China, and Propranalol Hydrochloride by Changzhou Yabang Pharmaceutical Company All other chemicals used were purchased from local commercial sources. Solutions and dilutions of all drugs were prepared in the distilled water.

Guinea pigs (500 to 600g) were housed at comfortable environment at room temperature. The tracheal tissue was taken out and rings of this tissue two to three mm wide are prepared, each having approximately 2 cartilages. A longitudinal cut was made on the ring to open it forming a preparation with smooth muscle in the centre and cartilaginous part on sides.. The tissue was mounted to an isolated tissue bath of 50 ml, capacity comprising of Kreb's Henseleit solution at 37º C and was having un interrupted oxygen supply. The smooth muscle contraction was recorded with an Isometric transducer (Harvard model no 72-4494) and was recorded on Oscillograph (Harvard model no 50-9307).

In group I, Cumulative dose-effect curves of bradykinin was observed with concentrations 22, 44, 66, 88, 110 and 132 µg/dl. Next dose is added after the peak has been achieved with first dose. In group II, cumulative concentration-effect curve of bradykinin was observed with similar concentrations of bradykinin but with the presence of captopril 10^{-5} concentration. In group III, same procedure repeated but in the presence of imidapril 10^{-5} concentration. In group IV, cumulative dose-effect curve of captopril was obtained using concentrations 1, 1.5, 2, 2.5 and 3 µM of captopril in the presence of set amount of bradykinin 66 µg/dl. This concentration of bradykinin has been chosen which causes consistent and submaximal effects, enabling us to observe potentiation or inhibition of contraction.[8] Maximum response of smooth muscle contraction with captopril 3 µM concentration was taken as hundred percent and effects with imidapril was compared to that.In group V, cumulative dose-response curve of imidapril was acquired using same concentrations the presence of fixed concentration of bradykinin 66 µg/dl. Experimentation was performed six times in the same way to get 6 observations in all the five groups.

Statistical analysis: The values were expressed as Means ± Standard deviation. The average of amplitudes of contractions and S.D were calculated using SPSS version 15. In order to find the significance of the difference between two observations 'student t test' was used. P value <0.05 was considered significant.

RESULTS

Captopril enhances the amplitude of tracheal contraction from mean value of 7.7 mm to 35.6mm Semi logarithm dose-effect curve of bradykinin with Captopril displaced to the left and upwards.

Imidapril at 10^{-5} M concentration also enhances tracheal smooth muscle contraction from mean value of 7.7mm to 17.1mm. Semi logarithm concentration response curve was shifted to left and upward.

In comparison of Control Group I (Bradykinin) and Group II (Captopril +Bradykinin) The mean values of response with each concentration of bradykinin, compared between Group I and II were found statistically significant showing P values of 0.003, 0.049, 0.05, 0.005, 0.019 and 0.00 as they are P<0.05.

In comparison of Control Group I (Bradykinin) and Group III (Imidapril + Bradykinin)

The mean values of response produced by each concentration of bradykinin used compared between Group I and Group III were found statistically significant (P <0.05) showing P values of 0.035, 0.021, 0.040, 0.035, 0.01 and 0.042. Comparison of concentration response curves of two drugs are shown in figure I.

In comparison of Group II (Captopril + Bradykinin) and Group III (Imidapril + Bradykinin**)** The mean values of responses produced by each concentration of bradykinin used compared between Group II and Group III were found statistically significant (P <0.05) showing P values of 0.012, 0.00, 0.001, 0.002, 0.002 and 0.007. Table 1

In the second set of experiments, bradykinin in a fixed concentration of 66µg/dl was added in the organ bath and then concentration-response curve was obtained by increasing concentration of Captopril. Same procedure was repeated with imidapril. This was done to determine the concentration-dependent response of two ACE inhibitors on contraction caused by bradykinin. The concentration of bradykinin (66µg/dl) was chosen because it produced consistent and submaximal effects enabling us to observe potentiation or inhibition of contraction. Results were similar to first set of experiments in which imidapril had produced less bradykinin-induced contraction than captopril. Imidapril produced least enhancement of the effect. Cumulative concentration-response curve with Captopril has been taken as the control and curve with Imidapril were compared to that. The shift of the curve is statistically significant (P<0.05) (figure II) Dusser et al, 1987, has reported similar effect with Captopril.

Table No.I: Comparison of responses to bradykinin between group II (bradykinin+ captopril 10^{-5} M) and group III (bradykinin + imidapril 10^{-5} M)

	Group II	Group III	Group II	Group III	Group II	Group III	Group II	Group III	Group II	Group III	Group II	Group III
Tissues	22 µg/dl	22 µg/dl	44 µg/dl	44 µg/dl	66 µg/dl	66 µg/dl	88 µg/dl	88 µg/dl	110 µg/dl	110 µg/dl	132 µg/dl	132 µg/dl
1	0	0	28	10	37	16	39	15	42	15	43	14
2	25	2	30	4	33	10	38	13	43	14	46	15
3	26	0	32	15	34	16	39	16	44	14	47	10
4	6	3	25	5	40	11	45	14	50	16	55	16
5	9	3	20	15	31	25	45	37	51	40	59	43
6	12	6	24	13	35	28	44	42	49	48	58	52
Mean	13 mm	2.33 mm	26.5 mm	10.33 mm	35 mm	17.67 mm	41.67 mm	22.83 mm	46.5 mm	24.50 mm	51.33 mm	25.00 mm
S.D	10.47	2.25	4.37	4.89	3.16	7.34	3.33	13.04	3.94	15.33	6.83	17.78
P value	0.012		0.00		0.001		0.002		0.002		0.007	

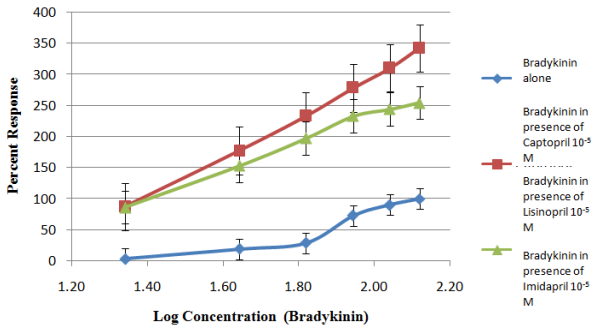

Figure No.I: Cumulative log dose-effect curves of bradykinin with fixed concentrations of captopril (10^{-5} M) and imidapril (10^{-5} M) separately.

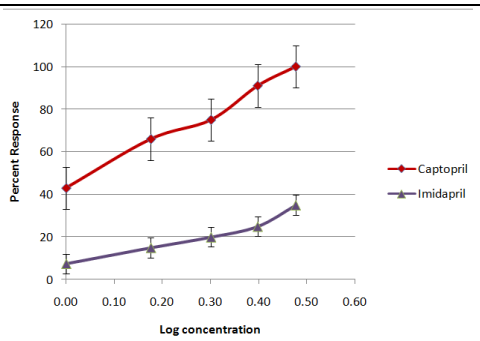

Figure No.2: Cumulative log dose-effect curves of Captopril and Imidapril with fixed concentration of bradykinin (66 µg/dl).

DISCUSSION

In this comparative study we had found that Imidapril produced significantly (P<0.05) less enhancement of bradykinin induced tracheal smooth muscle contraction than captopril. This was consistent with the results of previous studies.[8,9]

The mechanism by which ACE inhibitors potentiate kinin induced contraction is most likely by preventing the degradation of bradykinin. The enhancement of bradykinin-induced contraction by Angiotensin Converting enzyme inhibitors was also observed after having removed the tracheal epithelium. Therefore, this suggests that ACE is present in other tracheal tissues besides epithelium and these tissues may participate in the degradation of kinins in the airways. We can speculate that in a physiological situation, inactivation of kinins may occur at various sites within the airway, depending on the presence of the enzymes and on the sites from which kinins originate e.g diffusion of circulating kinin from plasma or local production within the airways.[8] Bradykinin causes tracheal smooth muscle contraction directly by stimulating distinct receptors, such as bradykinin acting on B_1 and B_2 receptors and indirectly by releasing mediator tachykinins (substance P and neurokinin A) and prostaglandins (PGs). B_1 receptors are mostly involved in inflammatory reaction.[9, 10]

ACE inhibitors differ chemically and based on that they have slightly different mechanism of actions. The enzyme is a zinc-metallopeptidase that have action on angiotensin II release and bradykinin degradation. ACE has 2 homologus domains categorized as C-part and N-part in relation to their propinquity to carboxylic or to amine terminal. Each part possesses a functionally active locus.[11] Both parts can cleave angiotensin I and bradykinin but it has been seen in experimental studies in mice that selective inhibition of either end domain of ACE can inhibit the transformation of Angiotensin I to Angiotensin II by the divergent selective blockers, whereas for blockade of bradykinin degradation, binding to both active ACE terminal sites is required[12]. Binding ability of ACE inhibitors to every part is not same in all inhibitors. It is to be found that difference in the degree of enhancement of bradykinin-induced vascular leakage is due to difference in binding abilities of drugs with angiotensin converting enzyme. The tendency of dry-cough with ACE Inhibitors is also variable due to same reason. Imidapril has nether role in these two effects than enalapril and captopril.[13] Activity of ACE inhibitors regarding substrate specificity were studied by Okamura et al. in 1993.[14] using mesenteric artery and vein of dog. They showed that imidaprilat, metabolite of imidapril has comparatively less inhibitory action on bradykinin degradation than enalaprilat.

Among ACE inhibitors used in the study captopril is active drugs while imidapril is a prodrug. It is an ester prodrug which is converted into active form imidaprilat by enzyme esterase.[15] Imidapril is converted to imidaprilat metabolically by carboxylesterase.[16] In vitro study conducted by Per Wetal et al in 1992 has shown carboxylesterase activity in respiratory system of guinea pig.[17] These studies show evidence that imidapril was converted into imidaprilat in the tracheal tissue. However the reason of lesser augmentation of bradykinin response by imidapril may be related to its incomplete activation in tracheal tissue.

Angiotensin converting enzyme (ACE) inhibitors are frequently used drugs for hypertension and heart failure.[18] They are safe and effective drugs for hypertension. After grand and well organized clinical studies (Consensus, Save, Trace, Aire, Hope and Europa studies) ACEI have become staple treatment for effective secondary prevention in patients with cardiovascular diseases and diabetic complications, unless contraindicated. However their use in some hypertensive individuals who concomitantly suffer from COAD, is restricted due to the production of cough and bronchoconstriction. The most important effect of bradykinin on the respiratory tract is the activation of C fibers in bronchial and pulmonary tissue, which is the cause of cough and chest tightness, an distinctive character of asthma.[19] In clinical trials it has been seen in patients that ACE inhibitors produce bronchospasm 2.39 times more then lipid lowering drugs.[20]

On the basis of different actions of ACE inhibitors we have performed the study to see the in vitro response of some commonly used ACE inhibitors on guinea pig's trachea. This in vitro study can provide us the basis for rational selection of an ACE inhibitor for patients with chronic obstructive airway disease.

CONCLUSION

Imidapril is found to cause least enhancement of contraction caused by bradykinin on tracheal muscle. Further clinical trials may be conducted to establish the differential effects of various clinically used ACE inhibitors on the respiratory passages in hypertensive patients concomitantly suffering from COAD.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Place and Duration of study

Designation of corresponding author, contact number and email address