ORIGINAL ARTICLE

IN VITRO RESPONSE OF TRACHEAL SMOOTH MUSCLE FROM HYPERRESPONSIVE GUINEA PIGS TO CELIPROLOL

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Background: The use of β-blockers is limited by adverse effects such as bronchospasm in asthmatics. Third generation β-blockers such as celiprolol may show better respiratory tolerability because they lack β-blocker induced broncho-constriction. **Method:** Effect of celiprolol on the histamine induced contraction of tracheal muscle strips prepared from ovalbumin-sensitised guinea pigs was studied. Using oxygenated Krebs-Henseleit solution as the nutrient medium, the trachealis muscle activity was measured with isometric force displacement transducer and recorded on 4-channel Oscillograph. **Result:** Celiprolol 10^{-4} M shifted the concentration-response curve of histamine downwards and to the right. Mean of amplitude of contraction, percent responses and deviations when compared with the control group were significantly different ($p<0.05$). **Conclusion:** Celiprolol antagonised histamine-induced contractions of tracheal muscle of guinea pigs. So it may be considered safe in patients with asthma. However, further clinical evaluation and exploratory work is required.

Keywords: Celiprolol, Histamine, Chronic Obstructive Airway Disease (COAD), Tracheal muscle

INTRODUCTION

Beta receptor blockers are one of the most effective drugs in treatment of cardiovascular as well as non-cardiovascular diseases. However controversies exist regarding the ability of these agents to induce bronchospasm in patients with COAD. Previous studies show that no β blocker is absolutely safe for asthmatic patients, but $\beta_1$selective blockers may have better respiratory tolerability though even they are not completely free of this adverse effect.[1]Celiprolol is cardioselective beta receptor antagonist with uniquely strong partial agonist activity at β_2 receptors and can exert a direct vasodilating and bronchodilating effect. Recent studies have shown that vasodilation is due to its ability to cause release of nitric oxide from endothelial cells.[2] However the ability of celiprolol to cause bronchodilation is still controversial since in some studies it worsened spirometric indices in patients with asthma.[3] So the present study was aimed to determine the effect of celiprolol on histamine-induced contraction in isolated sensitized tracheal muscle of guinea pigs.

MATERIAL AND METHODS

The present study was conducted on the isolated tracheal smooth muscle of guinea pigs of Dunkin Hartley variety weighing 500–600 gm. Ethics Committee approval of the protocol was obtained. The animals were given tap water *ad libitum* and were fed with a standard diet. Guinea pigs were sensitised to ovalbumin so as to create animal model of asthma and divided randomly into two groups. Development of sensitivity was confirmed by demonstration of Schultz-Dale reaction.[4] Krebs Henseleit solution was used as the nutrient solution the composition of which per 1,000 ml was: NaCl 118.2 mM, KCl 4.7 mM, $MgSO_4.7H_2O$ 1.2 mM, $CaCl_2$ 2.5 mM, KH_2PO_4 1.3 mM, $NaHCO_3$ 25.0 mM, Dextrose 11.7 mM. The trachea was obtained from guinea pigs and preserved in Kreb's solution. Rings, 2–3 mm wide were formed from it and cut into strips by a longitudinal cut on the ventral side opposite to the smooth muscle. The strip was then suspended in a tissue bath of 50 ml capacity, containing Kreb's solution at 37 ºC and was aerated with oxygen continuously. Its one end was attached to the oxygen tube while the other end was connected to an isometric force displacement transducer. The tissue was equilibrated for 45 minutes against an imposed tension of two grams. A tension of one gram was applied to the tracheal strip continuously throughout the experiments.[5] The trachealis muscle activity was recorded through the transducer on a 4-channel oscillograph by adding different concentrations of histamine with an interval of ten minutes between each concentration. Six experiments were performed and the mean response for each concentration was worked out. A concentration response curve was obtained by plotting the percent contraction against the logarithm of concentrations. In the second group tracheal muscle strips were pre-treated with fixed dose of celiprolol, i.e., 10^{-4} M for 15 minutes.[6] Same procedure was followed for different concentrations of histamine.

The results have been expressed as Mean±SEM using Microsoft Excel. The differences between the observations were considered significant if the *p*-value was less than 0.05 by using Student's *t*-test.

RESULTS

Mean±SEM values of the responses and the percent responses to different concentrations of histamine are shown in the tables. Percent response with 10^{-3} M of histamine was taken as 100%.

The difference in mean values of responses between Group 1 and Group 2 were found significant (p <0.05).The mean percent deviations for each dose of histamine used in Group 1 and Group 2 were 35.48, 19.10, 13.92, 8.82, and 9.38% respectively.

Table-1: Effect of histamine and celiprolol on ovalbumin sensitised isolated tracheal muscle of guinea pig (Group 1 & 2)

Histamine Concentration (M)	Groug-1		Group-2	
	Amplitude of Contraction (Mean±SEM)	Percent Response	Amplitude of Contraction (Mean±SEM)	Percent Response
10^{-7}	12.50±1.76	15.63	8.50±0.56	10.62
10^{-6}	33.16±1.57	41.46	26.83±1.49	33.54
10^{-5}	52.66±1.60	65. 83	45.33±2.38	56.66
10^{-4}	68.0±2.78	85	62.00±1.78	77.50
10^{-3}	80.0±2.56	100	72.50±1.70	90.62

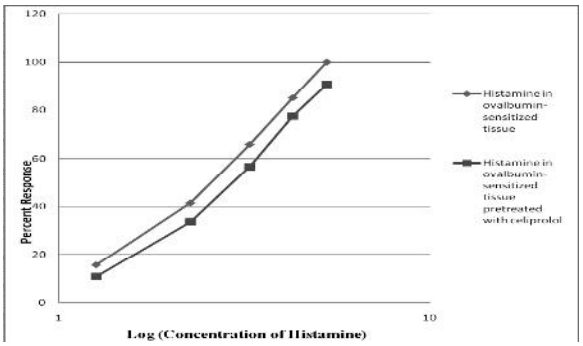

Figure-2: Log conc-response curves of histamine of ovalbumin-sensitised guinea pig tracheal muscle

DISCUSSION

Beta blockers which are valuable in the treatment of various diseases should be used with caution in patients with asthma.[1] Celiprolol, a β_1 selective blocker with partial agonist activity has been shown to have bronchodilating activity.[2] But also there are studies which have reported broncho-constriction with celiprolol in COAD patients.[3] So in the present study, the effect of celiprolol on sensitised tracheal muscle of guinea pig has been studied. The concentration-response curve of histamine was constructed in the presence of celiprolol in ovalbumin-sensitised tracheal muscle strips. The curve shifted downwards and to the right. The amplitude of contraction decreased with all the concentrations of histamine and all the parameters had p-value <0.05 which is considered as significant. It shows that celiprolol relaxed the sensitised tracheal smooth muscle of guinea pigs. These findings are in accordance with the findings of *in vivo* studies by Wheeldon *et al*,[7] Hauck *et al*,[8] and Doshan *et al*.[9] All of above mentioned studies were conducted in asthmatics, and showed relaxant effect of celiprolol on airway smooth muscle.

The mechanism underlying the effect of celiprolol on tracheal smooth muscle is still unclear. It may involve its β_1 selectivity but studies on highly cardio-selective beta blocker, bisoprolol, indicate that this selectivity does not contribute to bronchodilation. Isolated tissue studies suggest that weak α_2 blocking effect may also contribute to this bronchodilation but this property is not significant at therapeutic doses.[10] The partial agonist activity of celiprolol at β_2 receptors has also been implicated which seems plausible. Also according to recent studies modulation of nitric oxide by celiprolol may have some role in its property of bronchodilation.[2]

CONCLUSION

Celiprolol decreased the tone of sensitised tracheal muscle. Thus it may be considered a potential option for asthma patients when beta blockers are considered to be essential treatment. However additional clinical studies are required to verify the pulmonary effects of celiprolol.

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