Original Article

Cetirizine & Loratadine - Comparing Their Antagonist Effects on Isolated Trachea of Rabbit

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ABSTRACT

Objective: To study and compare the antagonist effects of Cetirizine and Loratadine on histamine induced contractions of isolated trachea of rabbit.

Study Design: Comparative controlled invitro experimental study.

Place and Duration of Study: This study was conducted at The Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC) Karachi, for the period of six months.

Materials and Methods: Isolated tracheal smooth muscles of twenty four rabbits were used. Fresh Kreb's nutritional solution was prepared for each subject. Tracheal smooth muscles were exposed to standard dilution of Histamine, and then they were challenged with serial dilutions (10^{-18} to 10^{-3} gm /ml) of *Cetirizine* and *Loratadine* separately. Responses as rate and amplitudes of contractions were recorded by 7B Grass Polygraph machine.

Results: Cetirizine inhibit the rate of histamine induced contractions of tracheal muscles from 0.85 to 12.33 % and amplitude from 0.0 to 82.69 %, as concentration of drugs increased. While Loratadine inhibit the rate of histamine induced tracheal contractions from 0.85 to 10.59 % and amplitude from 6.5 to 76.82 % as concentration of drugs increased.

Conclusion: Cetirizine found more potent than Loratadine as inhibitor of histamine induced contraction in isolated tracheal smooth muscles of rabbit.

Category: Basic Sciences.

Key Words: Cetirizine, Loratadine and Tracheal smooth muscles.

INTRODUCTION

Seasonal allergic rhinitis is a common disease world wide affecting a significant percentage of the global population. It is a source of great discomfort, and can have a major effect on patient's quality of life. Indeed more than 90% of seasonal allergic rhinitis patients believe that their work productivity is negatively affected by allergy symptoms [1,2].

Histamine is generally considered as the principle mediator of acute inflammatory process and allergic reaction [3], in both the upper and lower respiratory airways [4]. It has important role in gastric acid secretion and function as neurotransmitter and neuromodulator [5]. Histamine is found in all tissues, but in high amount in lungs, skin, gastrointestinal tract mast cells and basophils [6]. It is also found in animals, in plants, as a component of venoms and secretions from insect stings [7]. The effects of histamine are exerted through three well defined classical G protein coupled histamine receptor subtypes termed H_1R, H_2R and H_3R, and the more recently H_4R. Histamine signaling through H_1R is responsible for the majority of the immediate manifestations of allergic disease [8].

Anti-histamines are the classic H_1 receptors mediated response blockers and competitively block the receptor mediated response of target tissues [9]. They are divided into first and second generation anti-histamines. The main distinguishing points between first and second generation anti-histamines are that first generation drugs are widely distributed throughout the body and are more likely to block autonomic receptors and enter the central nervous system readily, while the second generation drugs are less lipid soluble and enter the central nervous system with difficulty or not at all, so they show less sedative and anticholinergic effects [10].

Cetirizine: It is a potent, non-sedative, H_1 receptor antagonist belongs to second generation antihistamines [2, 8]. It is a member of piperizine group of H_1 antagonists[11]and pharmacologically active oxidized metabolite of hydroxyzine. It is minimally metabolized so it may be anti-histamine of choice for patients with hepatic dysfunction and can also be used in elderly patients without dosage reduction. It has a low rate of penetration of the blood brain barrier and is without any significant anti-cholinergic and anti-serotonin effects, used in the treatment of allergy[12].

Loratadine: It is highly potent[3], non-sedative and long acting tricyclic[13], second generation anti-histamine[14], with selective competitive peripheral histamine H_1 receptor antagonistic activity[15], belonging to the pipridine group and structurally related to azatadine[16]. It

is less lipophilic, has no central nervous system activity and is essentially free of sedation[17]. It is proven to be effective in the treatment of seasonal allergic rhinitis, chronic idiopathic urticaria and allergic bronchial asthma[18, 19].

Purpose of study:

The purpose of study was to evaluate and compare the antagonistic effects of Cetirizine and Loratadine on histamine induced contractions of isolated tracheal smooth muscles of rabbit.

MATERIALS AND METHODS

All experimental work was carried out for the period of six months, in the Department of Pharmacology and Therapeutics, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC), Karachi.

Preparation of serial dilutions of drugs: Serial dilutions were made by taking 1 ml of drug and adding 9ml of distilled water to make the ratio 1:9 .In this way serial dilutions of drugs were prepared from concentration 10^{-3} to 10^{-18} gm/ml.

Nutrition solution: In this vitro project Kreb's bicarbonate nutritional solution was used for the perfusion of isolated tracheal tissue. For the preparation of 5 liters of Kreb's bicarbonate solution, following quantities of ingredients were used: Sodium chloride 34:50 gm, Sodium bicarbonate 10.50 gm, D-glucose 10.00 gm, Sodium dihydrophosphate 0.60 gm, Potassium chloride 1.85gm, Magnesium chloride 0.23 gm, Distilled water 5000 ml.

Preparation and isolation of tracheal smooth Muscle: Twenty-four healthy adult rabbits male and female (non-pregnant), approximately 2kg weight were selected and used for the present study. The animals were sacrificed; trachea was removed and transferred to Petri dish containing aerated (oxygenated) Kreb's bicarbonate solutions, where it was cleaned of extraneous tissues. A chain of tracheal section was made by cutting several rings of cartilages and tying them together loosely in such a way that muscles of two rings were at 180^{0} to each other. Chain was suspended vertically in an inner organ bath containing 20 ml Kreb's bicarbonate solution with the help of tissue holder and connected to the 7B Grass Polygraph machine with the help of force transducer. The nutritional solution was continuously aerated 10-12 bubbles of oxygen per minutes and temperature was equilibrate in Kreb's bicarbonate solution for 90 minutes. Bath solution was changed after every 15 minutes. The drugs were added in small quantities (1ml) at each interval to inner organ bath from lower concentration 10^{-18} gm/ml to higher concentration 10^{-3} gm/ml according to experimental protocol and response from each dilution was recorded on Grass Polygraph under resting tension of 1 gm.

Method: Experimental subjects were divided into three groups. Eight animals were used in each group and eight experiments were done in each group. The responses were recorded as Rate and Amplitude of isolated tracheal smooth muscle contractions

In group-I, first of all spontaneous contractions of tracheal smooth muscles were recorded than tissue were challenged with a serial dilutions of histamine (from 10^{-18} to 10^{-3} gm/ml) and responses were recorded. From these responses, standard concentration of histamine (10^{-3} gm/ml) was selected, which had produced maximum response.

In group-II, tissues were challenged with serial dilutions of Cetirizine (from10^{-18} to 10^{-3} gm/ml) in the presence of selected standard concentration of histamine (10^{-3} gm/ml) and responses were recorded for each dilution. After taking response of each concentration the tissues were washed and given rest for 3 minutes before applying the next concentration.s

In group III, tissues were challenged with serial dilutions of Loratadine (from 10^{-18} to 10^{-3} gm/ml) in the presence of selected standard concentration of histamine (10^{-3} gm/ml) and responses were recorded for each dilution. After taking response of each concentration the tissues were washed and given rest for 3 minutes before applying the next concentration.

RESULTS

Effects of Cetirizine on Histamine Induced Contractions in Isolated Tracheal smooth muscles of rabbit (Group-II):

Rate: Cetirizine antagonized the rate of histamine induced contractions of isolated tracheal smooth muscles from 0.85 % to 3.70 % non-significantly at the concentrations 10-18 to 10-12 gm/ml and from 7.78 % to 12.33 % significantly ($p<0.001$) at concentrations 10-11 to 10-3 gm/ml. (Table No.1).

Amplitude: Cetirizine antagonized the amplitude of histamine induced contractions of isolated tracheal smooth muscles 0.00 % to 13.33 % non-significantly at the concentrations 10-18 to 10-12 gm/ml and from 30.30 % to 82.69 % significantly ($p<0.001$) at concentrations 10-11 to 10-3 gm/ml. (Table No.2)

Effects of Loratadine on Histamine Induced Contractions in Isolated Tracheal smooth muscles of rabbit (Group-III):

Rate: Loratadine antagonized the rate of histamine induced contractions of tracheal smooth muscles from 0.85 % to 5.75 % non-significantly at the concentrations 10-18 to 10-11 gm/ml and from 7.52 % to 10.59 % significantly ($p<0.001$) at concentrations 10-10 to 10-3 gm/ml. (Table No.3)

Amplitude: Loratadine antagonized the amplitude of histamine induced contractions of tracheal smooth muscles from 0.00 to 8.89 % non-significantly at the

concentrations 10-18 to 10-13 gm/ml and from 15.69 % to 76.82 % significantly (p<0.001) at concentrations 10-12 to 10-3 gm/ml. (Table No.4)

Table No.1: Effects of Citirizine on Histamine induced Contractionsin Isolated Trachea of Rabbit (Group-II) (Rate of contraction)

Drug concentration	Agonist		Antagonist		Agonist to antagonist	
gm/ml	Mean	SEM	Mean	SEM	%age	P-value
10^{-18}	29.37	0.46	29.62	0.49	0.85	n.s
10^{-17}	30.87	0.47	30.87	0.47	0.00	n.s
10^{-16}	32.37	0.56	32.12	0.47	0.77	n.s
10^{-15}	35.5	0.46	33.25	0.49	1.33	n.s
10^{-14}	34.5	0.46	34.12	0.44	2.72	n.s
10^{-13}	35.37	0.46	35.00	0.46	3.46	n.s
10^{-12}	36.37	0.41	35.25	0.52	3.70	<0.01
10^{-11}	36.37	0.47	34	0.70	7.78	<0.001
10^{-10}	37.12	0.54	34.62	0.49	9.42	<0.001
10^{-9}	38.00	0.42	35	0.46	7.89	<0.001
10^{-8}	39.00	0.53	35.25	0.70	9.19	<0.001
10^{-7}	39.37	0.53	35.75	0.75	9.19	<0.001
10^{-6}	39.5	0.62	35.37	0.62	10.45	<0.001
10^{-5}	39.25	0.61	35.37	0.82	9.85	<0.001
10^{-4}	39	0.42	34.37	0.59	11.87	<0.001
10^{-3}	38.5	0.46	33.75	0.61	12.33	<0.001

Table No.2: Effects of Citirizine on Histamine induced Contractions in Isolated Trachea of Rabbit (Group-II) (Amplitude of contraction)

Drug concentration	Agonist		Antagonist		Agonist to antagonist	
gm/ml	Mean	SEM	Mean	SEM	%age	P-value
10^{-18}	2.12	0.12	2.12	0.12	0.00	n.s
10^{-17}	2..87	0.12	2.87	0.12	0.00	n.s
10^{-16}	4.12	0.22	4.12	0.12	0.00	n.s
10^{-15}	5.37	0.18	5.37	0.22	0.00	n.s
10^{-14}	6.12	0.22	6.12	0.18	0.00	n.s
10^{-13}	6.87	0.22	6.87	0.22	0.00	n.s
10^{-12}	7.5	0.18	6.5	0.22	13.33	n.s
10^{-11}	8.25	0.25	5.75	0.18	30.30	<0.001
10^{-10}	9.12	0.22	5.62	0.16	38.04	<0.001
10^{-9}	9.62	0.18	5.25	0.18	45.42	<0.001
10^{-8}	10.37	0.18	4.5	0.16	56.60	<0.001
10^{-7}	11.12	0.12	4.12	0.18	62.94	<0.001
10^{-6}	11.87	0.12	3.87	0.12	67.79	<0.001
10^{-5}	12.00	0.00	3.37	0.12	71.91	<0.001
10^{-4}	12.00	0.00	2.62	0.18	77.5	<0.001
10^{-3}	12.25	0.16	2.12	0.12	82.69	<0.001

DISCUSSION

We have observed the effects of Cetirizine and Loratadine on histamine induced contractions of isolated tracheal smooth muscles. We found that Cetirizine has more potent antagonistic action than Loratadine on rates and amplitudes of histamine induced contractions of isolated tracheal smooth muscles. Our observations are in correlation with the results of study of Dobashi (1995), in which he found that cetirizine antagonize the histamine induced contractions in a concentration dependent fashion on smooth muscles of isolated trachea of rabbit [20]. Our results confirmed by the findings of Liu H (2005) study, who observed antagonistic effects of antihistamines on muscarinic induced mucus cell ion

Table No.3: Effects of Loratadine on Histamine induced Contractions in Isolated Trachea of Rabbit (Group-III): (Rate of contraction)

Drug concentration	Agonist		Antagonist		Agonist to antagonist	
gm/ml	Mean	SEM	Mean	SEM	%age	P-value
10^{-18}	29.37	0.49	29.62	0.37	0.85	n.s
10^{-17}	30.25	0.55	30.37	0.46	0.39	n.s
10^{-16}	31.5	0.62	31.37	0.53	0.41	n.s
10^{-15}	31.87	0.54	31.87	0.54	0.00	n.s
10^{-14}	33.75	0.86	33.25	0.61	0.74	n.s
10^{-13}	35.37	0.77	34.25	0.64	3.16	n.s
10^{-12}	36.37	0.70	35	0.5	3.76	n.s
10^{-11}	37	0.63	34.87	0.69	5.75	<0.01
10^{-10}	38.12	0.54	35.25	0.55	7.52	<0.001
10^{-9}	38.37	0.67	35.37	0.77	7.81	<0.001
10^{-8}	39.25	0.52	36	0.59	8.28	<0.001
10^{-7}	39.37	0.62	36	0.62	8.55	<0.001
10^{-6}	39.25	0.61	36	0.59	8.28	<0.001
10^{-5}	39.12	0.83	35.25	0.75	9.89	<0.001
10^{-4}	38.5	0.73	34.62	0.65	10.05	<0.001
10^{-3}	37.75	0.64	33.75	0.64	10.59	<0.001

Table No.4: Effects of Loratadine on Histamine induced Contractions in Isolated Trachea of Rabbit (Group-III): (Amplitude of contraction)

Drug concentration	Agonist		Antagonist		Agonist to antagonist	
gm/ml	Mean	SEM	Mean	SEM	%age	P-value
10^{-18}	2.00	0.00	1.87	0.12	6.5	n.s
10^{-17}	2.50	0.18	2.50	0.18	0.00	n.s
10^{-16}	3.62	0.18	3.62	0.18	0.00	n.s
10^{-15}	4.5	0.18	4.5	0.18	0.00	n.s
10^{-14}	5.25	0.16	5.25	0.16	0.00	n.s
10^{-13}	5.62	0.18	4.87	0.29	8.89	<0.01
10^{-12}	6.37	0.18	5.37	0.18	15.69	<0.001
10^{-11}	7.62	0.18	5.37	0.18	29.52	<0.001
10^{-10}	8.25	0.16	4.87	0.29	44.35	<0.001
10^{-9}	8.62	0.18	5.12	0.22	40.60	<0.001
10^{-8}	9.37	0.26	4.87	0.22	48.02	<0.001
10^{-7}	9.87	0.12	4.62	0.18	53.19	<0.001
10^{-6}	10.12	0.12	4.25	0.16	58.00	<0.001
10^{-5}	10.75	0.16	4.00	00	64.28	<0.001
10^{-4}	11.62	0.18	3.75	0.16	67.72	<0.001
10^{-3}	11.87	0.12	2.87	0.12	76.82	<0.001

transport and rank them on potency in order to Desloratadine > Cetirizine > Fexofenadine > Diphenhydramine > Loratadine[21.] Our observations were in complete agreement with the study of Meltzer EO (1996), who observed that cetirizine provided greater relief of allergic rhinitis symptoms caused by outdoor allergent compared with loratadine [12]. Day JH (1998) also found in his study that cetirizine is more effective in reducing symptoms of seasonal allergic rhinitis than that of loratadine[18].

CONCLUSION

In this present in vitro study, we have observed the effects of second generation anti-histamines Cetirizine and Loratadine on histamine induced contractions of isolated tracheal smooth muscles. We found that Cetirizine has more potent antagonistic action than Loratadine on histamine induced contractions of tracheal smooth muscles.

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