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Relaxant effect of pioglitazone on the guinea-pig isolated trachea through the modulation of endogenous prostaglandins

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ABSTRACT

Thiazolidinediones are commonly used anti-diabetic drugs. Owing to the anti-inflammatory action of TZDs as a result of there action on the PPAR gamma receptor and a proposed action on the prostaglandins, these drugs can be tried in the acute exacerbations of COPD that are also commonly found among diabetic patients. An experimental study of one week was carried out at animal house of Army Medical College, Rawalpindi on a total of 50 guinea pigs (both male and female) of Dunkin Hartley variety, weighing 500 to 600 grams. An isometric volume transducer was used to measure the histamine induced contractions of the smooth muscles. In the similar way contractions with pioglitazone in the presense of histamine, contractions with indomethacin which is a prostaglandin antagonist, in the presence of histamine and mixed effect of pioglitazone along with indomethacin in the presence of histamine was evaluated. Pioglitazone produced significant reduction in histamine-induced contractions of the normal tracheal muscle strips thus identifying its relaxant effect on the tracheal smooth muscles. The contractions of the tracheal muscles were increased when indomethacin was used. The pioglitazone induced relaxation was also reduced in the group pre-treated with indomethacin, thus suggesting an identifiable role of prostaglandins in the relaxant effect of TZDs on the smooth muscles.

Keywords
Diabetes, Chronic obstructive pulmonary disease (COPD), Thiazolidinediones, Pioglitazone, Endogenous prostaglandins

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has recently been estimated to affect around 328 million people worldwide, i.e. 168 million men and 160 million women [1]. By 2010, COPD was rated as the third most common cause of death worldwide with total estimated deaths of 2.8 million in 2010 [2]. The most concerning issue related to COPD are the acute exacerbations [3]. These exacerbations have many causative factors. According to recent study type 2 diabetes mellitus (T2DM) related chronic inflammation leads to the COPD exacerbations [4]. T2DM leads to glucotoxicity, lipotoxicity as well as oxidative stress that lead to the modulation of the inflammatory responses [5]. These processes induce the pro-inflammatory response that coexist with the deranged pulmonary function marked by a reduced vital capacity and other lung functions even in the absence of other exacerbating factors [6]. Patients suffering from COPD have a greater tendency (around 18.7%) of developing T2DM as compared to the general population (about 10.5%) [7]. This is most probably as a result of common pathophysiological soil between these two including a reduced pulmonary function resulting from the glycosylated pulmonary proteins, thickened lamina basalis, enhanced propensity to infections [8] and the hyper responsiveness of the bronchi to the contractile agents owing to the exposure to high glucose concentrations [9].

Hypoglycemic drugs can improve the pulmonary function not only by correcting dysmetabolism but also as a result of their pleiotropic effects that can reduce inflammation and oxidative stress [10]. One of the oral hypoglycemic groups of drugs that are known to possess the anti-inflammatory activity is Thiazolidinediones (TZDs) [11]. This group includes drugs such as rosiglitazne, pioglitazone, citoglitazone etc [12]. These drugs act as agonists of a transcription factor known as proliferator activated receptor gamma (PRAPγ) [13]. PRAPγ plays an inhibitory role in both the synthesis as well as the release of inflammatory cytokines through regulation of gene expression via retinoid X receptor [14]. Thiazolidinediones are also thought to modulate endogenous prostaglandins leading to the anti-inflammatory response [15].

These medications can hence prevent the COPD exacerbations along with providing diabetic control. In addition, for the patients not suffering from T2DM these drugs can decrease the use of inhaled corticosteroids. Since not only that the steroid treatment in these patients is not always successful but can also lead to a number of adverse reactions in these patients [16].

In addition these medicines can be used as a treatment option in cases where the steroid therapy either fails or cannot be given owing to the adverse effects associated with the steroids [17]. Therefore, pioglitazone if used in asthma is not only going to decrease the incidence of asthmatic episodes and reduce the number and severity of exacerbations but also lead to a decreased use of the corticosteroid therapy [18].

The purpose of this study was to assess the anti-inflammatory action of pioglitazone on the tracheal smooth muscles and to assess the involvement of prostaglandins by using Indomethacin that is a prostaglandin inhibitor.

MATERIAL AND METHODS

The present study has been conducted on the isolated tracheal smooth muscle of 50 guinea pigs (both male and female) of Dunkin Hartley variety [19] weighing 500 to 600 grams They were housed at animal house of Army Medical College, Rawalpindi at room temperature. The animals were given tap water and were fed twice a day with a standard diet consisting of high-quality guinea pig hay, pelleted guinea pig food and small amounts of fresh vegetables and fresh fruit. They were kept in 12 hours/light 12 hours/dark cycle and allowed to acclimatize for a week before starting the experiments. The pigs were randomly divided into 5 groups of 6 pigs each. Group 1 was taken as the histamine control group, group 2 was given indomethacin, group 3 pioglitazone plus indomethacin and group 5 received increasing concentrations of pioglitazone.

The guinea pigs were killed by cervical dislocation [20]. Chest was opened through midline incision. The whole of trachea, from larynx to bronchi, was dissected out and transferred to a dissecting dish containing Kreb's Henseleit solution at room temperature. The tracheal tube was cut into rings, two to three millimeter (mm) wide, each containing about two cartilages. Each ring was opened by a longitudinal cut on the ventral side opposite to the smooth muscle, forming a tracheal chain with smooth muscle in the centre and cartilaginous portion on the edges. The tissue preparation was then transferred to an isolated tissue bath of 50 ml capacity, containing Kreb's Henseleit solution at 37ºC and was aerated with oxygen continuously. One end of the tracheal strip was attached to the lower end of the oxygen tube inside the tissue bath while the other end was connected to a research grade isometric force displacement transducer Harvard model No 72-4494, by means of a thread. Tissues were secured such that the alignment of the muscle contraction is with the vertical plane between the anchoring hook below and transducer above. The tissue was allowed a period of equilibration for 45 minutes against an imposed tension of two grams. During this period, the physiological solution in the organ bath was changed three to four times. A tension of one gram was applied to the tracheal strip continuously throughout the experiment after the initial equilibration period. The trachealis muscle activity was recorded through the isometric force displacement transducer on four channel oscillograph Harvard model No 50-9307.

Isometric force displacement transducer is meant to measure isometric contraction force without motion. This transducer measures force by measuring change in the capacitance of a stiff beam between two plates. The statistical analysis was performed through post hoc tukey test using SPSS version 22.

RESULTS

Group 1- Histamine Control (Effect of Histamine on Isolated Tracheal Muscle of Guinea Pig)

Effects of histamine were studied on isolated guinea pig tracheal muscle by adding different concentrations of histamine. Histamine produced concentration dependent contractions of the isolated tracheal muscle strips (Figure 1). In a series of six experiments, the mean ± standard error of mean (SEM) values of the response to the different concentrations of histamine. Percent responses were calculated for all of the above mentioned concentrations of histamine, taking the response with 10-3 M as 100 percent (Table 1). The semi-log concentration response curve of histamine was constructed by plotting the percentage responses against the log concentration and is shown in Figure 2.

Group 2- Effect of Fixed Concentration of Pioglitazone (100 μM) on Concentration Response Curve of Histamine on Isolated Tracheal Muscle of Guinea Pig

Pioglitazone produced significant change in histamine-induced contractions of the normal tracheal muscle strips (Figure 3). In a series of six experiments performed on the

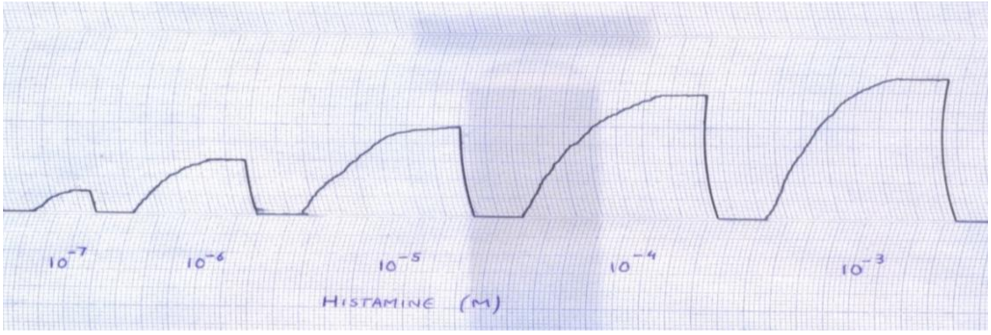

Figure 1. Concentration response curve of histamine on isolated tracheal muscle of guinea pig (n=6). One small square = 10 mm on the vertical axis.

Table 1. Group 1 (Response of isolated tracheal muscle of guinea pig to histamine)

Concentration (M) of Histamine	Amplitude of Contraction (mm ± S.E.M) n = 6	Percent (%) Response
10^{-7}	11.17 ± 0.65	14.29
10^{-6}	30.5 ± 1.63	39.02
10^{-5}	49.67 ± 0.71	63.54
10^{-4}	65.33 ± 1.98	83.58
10^{-3}	78.17 ± 1.30	100

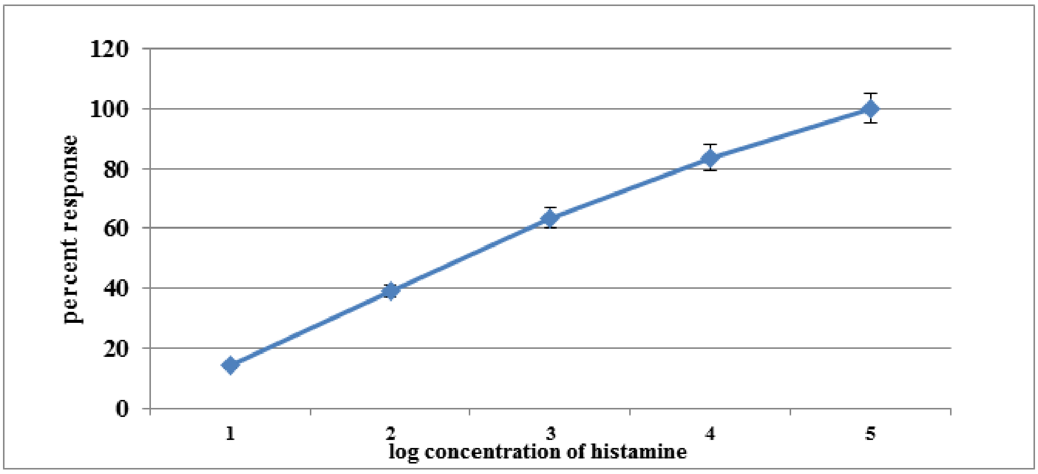

Figure 2. Log concentration response curve of histamine on isolated tracheal muscle of guinea pig. Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

strips pretreated with pioglitazone (100 µM) b (Table 4). Percent responses were calculated for the above mentioned concentrations of histamine (Table 2). The semi-log concentration response curve of histamine in the presence of pioglitazone was constructed by plotting the percentage responses against the log concentrations and is shown in Figure 4.

Group 3- Effect of Indomethacin (10 µM) on Concentration Response Curve of Histamine on Isolated Tracheal Muscle of Guinea Pig

In a series of six experiments performed on the isolated tracheal muscle strips pretreated with indomethacin 10 µM, the mean ± SEM values of the responses to the different concentrations of histamine (Figure 5). Percentage responces were calculated (Table 3). The semi-log concentration response curve of histamine in presence of indomethacin was constructed by plotting the percentage responses against the log concentration and is shown in Figure 6.

Group 4- Effect of Indomethacin (10 µM) in the Presence of Fixed Concentration of Pioglitazone (100 µM) on Concentration Response Curve of Histamine on Isolated Tracheal Muscle of Guinea Pig

In a series of six experiments performed on the isolated tracheal muscle strips pretreated with 10 µM indomethacin and 100 µM pioglitazone, the mean ± SEM values of the responses to the different concentrations of histamine. The mean percent responses were calculated (Table 4). The semi-log concentration response curve of histamine in presence of

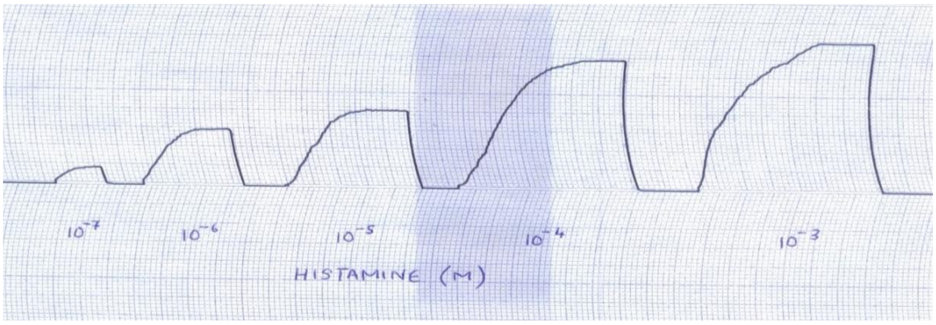

Figure 3. Concentration response curve of histamine in the presence of fixed concentration of pioglitazone (100 µM) on isolated tracheal muscle of guinea pig (n=6). One small square = 10 mm on the vertical axis.

Table 2. Group 2 (Response of isolated tracheal muscle of guinea pig to histamine in presence of fixed concentration of pioglitazone)

Concentration (M) of Histamine	Amplitude of contraction (mm ± S.E.M) n = 6	Percent (%) Response
10^{-7}	8.17 ± 0.54	10.45
10^{-6}	27.83 ± 1.25	35.61
10^{-5}	44.17 ± 1.25	56.50
10^{-4}	64.33 ± 1.50	82.30
10^{-3}	75 ± 1.57	95.95

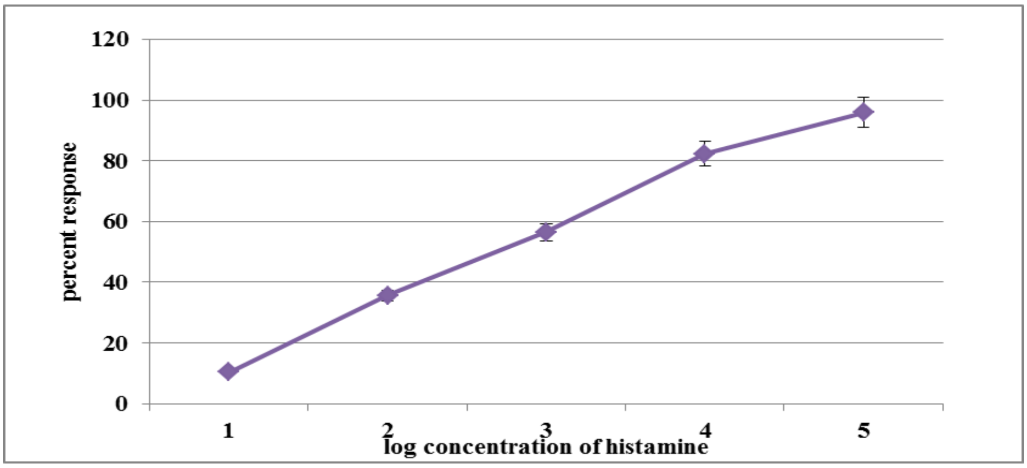

Figure 4. Log concentration response curve of histamine in the presence of fixed concentration of pioglitazone (100 µM) on isolated tracheal muscle of guinea pig. Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

indomethacin and pioglitazone was constructed by plotting the percentage responses against the log concentration and is shown in Figure 8.

Group 5- Effect of Increasing Concentration (10-100 µM) of Pioglitazone on Resting Tension of Isolated Tracheal Muscle of Guinea Pig

Effects of pioglitazone were studied on isolated guinea pig tracheal muscle by adding different concentrations of pioglitazone. Pioglitazone produced concentration dependent relaxation of the isolated tracheal muscle strips (Figure 9). In a series of six experiments, the mean ± SEM values of the responses to the different concentrations of pioglitazone. Percent responses were calculated for all of the above mentioned concentrations of pioglitazone, taking the response with 100 µM of salbutamol as 100 percent (Table 5). The semi-log concentration-response curve of pioglitazone was constructed by plotting the percentage responses against the log concentration and is shown in Figure 10.

Comparative observations of the groups

Comparison of Group 1 (Histamine control) with

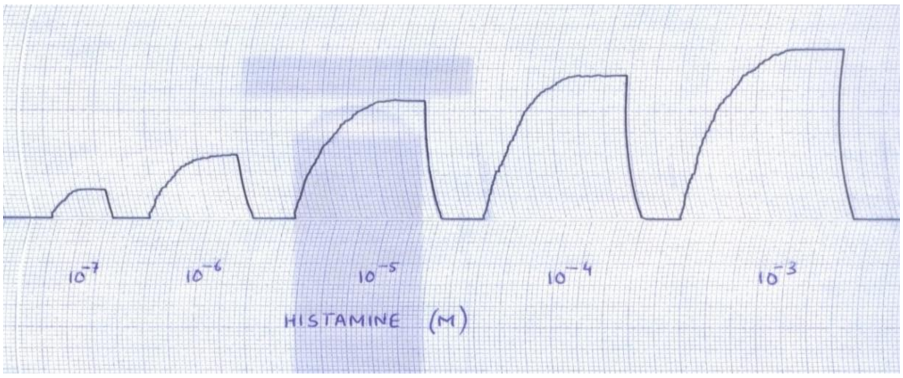

Figure 5. Concentration response curve of histamine in the presence of fixed concentration of indomethacin (10 µM) on isolated tracheal muscle of guinea pig (n=6). One small square = 10 mm on the vertical axis

Table 3. Group 3 (Response of isolated tracheal muscle of guinea pig to histamine in presence of fixed concentration of indomethacin)

Concentration (M) of Histamine	Amplitude of Contraction (mm ± S.E.M) n = 6	Percent (%) Response
10^{-7}	11.5 ± 0.56	14.71
10^{-6}	29.33 ± 2.03	37.53
10^{-5}	50.33 ± 0.99	64.39
10^{-4}	63.5 ± 1.18	81.24
10^{-3}	77.67 ± 0.49	99.36

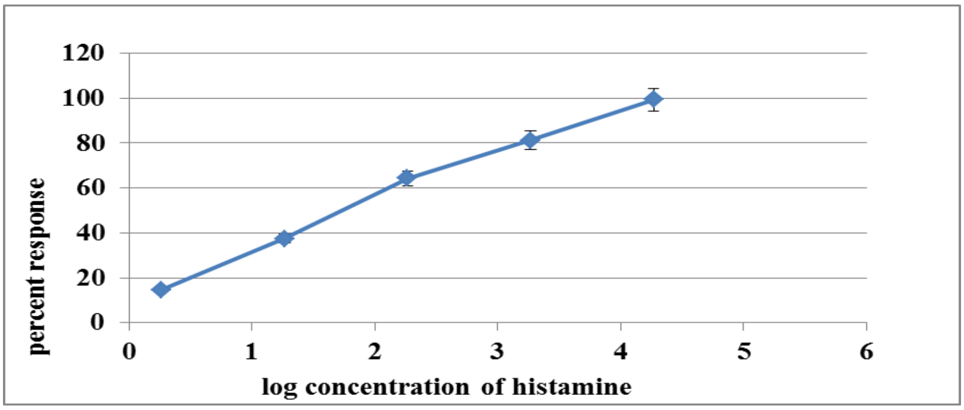

Figure 6. Log concentration response curve of histamine in the presence of fixed concentration of indomethacin (10 µM) on isolated tracheal muscle of guinea pig. Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM

Group 2 (Histamine after Pretreatment with Pioglitazone)

The mean values of responses produced by concentrations of 10^{-7}, 10^{-6} and 10^{-5} M of histamine when compared between Group 1 and Group 2 were found statistically significant (P<0.05) but non-significant at 10^{-4} and 10^{-3} M (P<0.05). The mean percent responses calculated at each of the above mentioned doses of histamine when compared between Group 1 and Group 2 were found statistically significant (P < 0.05). The mean percent deviations were calculated for each dose of histamine used in Group 1 and Group 2 and were 31.07, 9.15, 11.74, 1.54 and 4.14 percent respectively. The mean deviation was 11.53 percent.

Comparison of Group 1 (histamine control) with Group 3 (histamine after pretreatment with indomethacin

The mean values of responses produced by different concentrations of histamine when compared between Group 1 and Group 3 were found statistically non-significant (P > 0.05). The mean percent responses calculated at each of the above mentioned doses of histamine when compared between Group 1 and Group 3 were found statistically non-significant (P> 0.05). The mean percent deviations were cal-

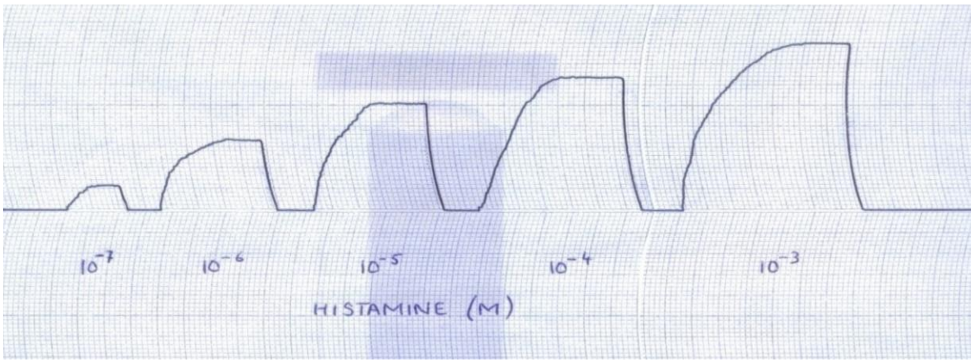

Figure 7. Concentration response curve of histamine in the presence of fixed concentration of indomethacin (10 µM) and pioglitazone (100 µM) on isolated tracheal muscle of guinea pig (n=6). One small square = 10 mm on the vertical axis

Table 4. Group 4 (Response of isolated tracheal muscle of guinea pig to histamine in presence of fixed concentration of indomethacin and pioglitazone)

Concentration (M) of Histamine	Amplitude of Contraction (mm ± S.E.M) n = 6	Percent (%) Response
10^{-7}	10.83 ± 0.48	13.86
10^{-6}	30.83 ± 0.87	39.45
10^{-5}	50.83 ± 1.08	65.03
10^{-4}	65.33 ± 0.67	83.58
10^{-3}	79.50 ± 0.85	101.71

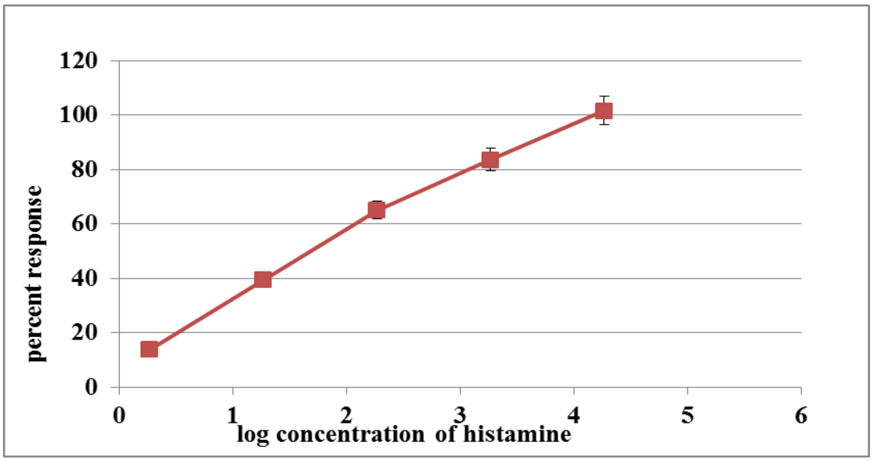

Figure 8. Log concentration response curve of histamine in the presence of fixed concentration of indomethacin (10 µM) and pioglitazone (100 µM) on isolated tracheal muscle of guinea pig. Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

culated for each dose of histamine used in Group 1 and Group 3, and were 2.95, 3.91, 1.34, 2.83 and 0.64 percent respectively. The mean deviation was 0.62 percent.

Comparison of Group 2 (histamine after pretreatment with pioglitazone) with Group 4 (histamine after pretreatment with indomethacin and pioglitazone)

The mean values of responses produced by different concentrations of histamine were found statistically significant ($P < 0.05$). The mean percent responses calculated at each of the above mentioned doses of histamine when compared between Group 2 and Group 4 were found statistically significant ($P < 0.05$). The mean percent deviations were calculated for each dose of histamine used in Group 3 and Group 7 and 40.72, 27.68, 17.85, 20.22 and 13.90 were percent respectively. The mean deviation was 24.08 percent.

DISCUSSION

We have studied the effects of pioglitazone on the histamine-induced contractions and explored the involvement of prostaglandins in the smooth muscle relaxation produced by pioglitazone by using a prostaglandin inhibitor, indomethacin.

In the first set of experiments, effects of different con-

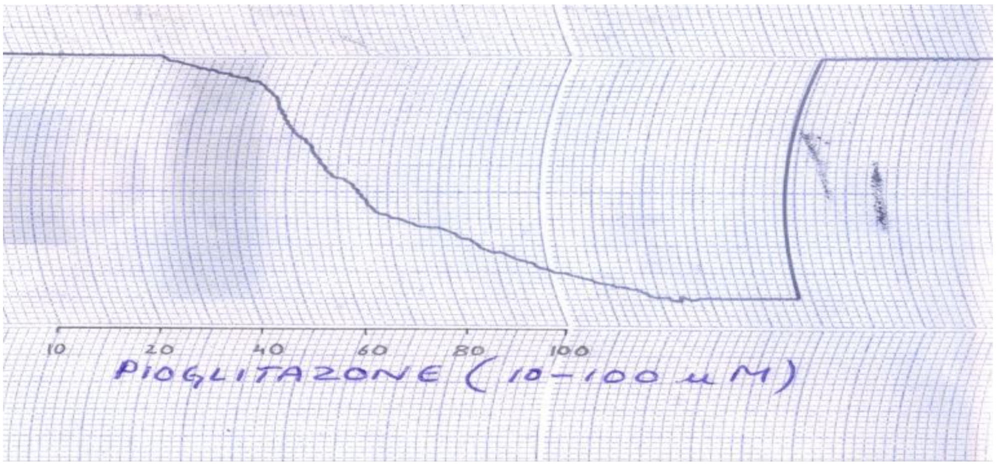

Figure 9. Concentration response curve of increasing concentration of pioglitazone (10-100 µM) on isolated tracheal muscle of guinea pig (n=6). One small square = 10 mm on the vertical axis

Table 5. Group 5 (Response of isolated tracheal muscle of guinea pig to increasing concentration of pioglitazone)

Concentration (M) of pioglitazone	Amplitude of Relaxation (mm ± S.E.M) n = 6	Percent (%) Response
10	0 ± 0	0
20	15 ± 1.63	16.73
40	43.5 ± 1.50	48.51
60	59.17 ± 1.62	65.99
80	76.83 ± 0.91	85.69
100	88.83 ± 1.11	۹۹,۰۷

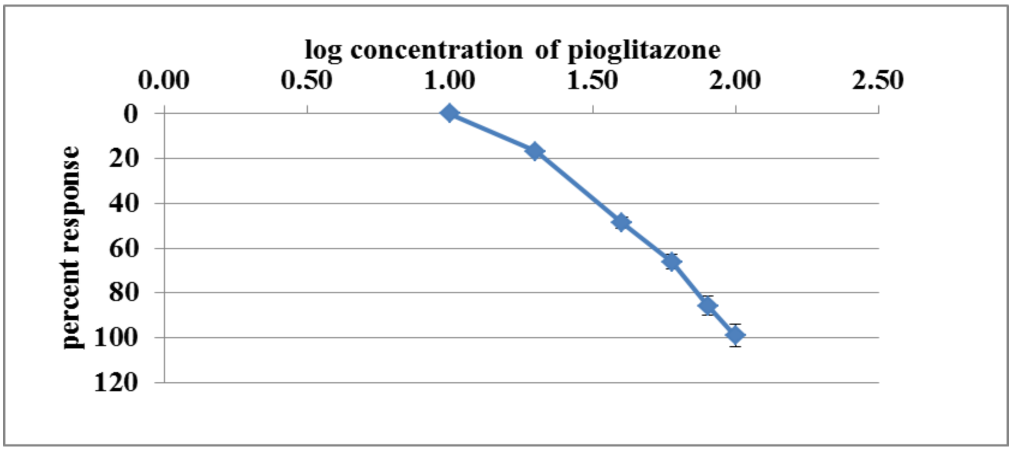

Figure 10. Cumulative log concentration response curve of increasing concentration of pioglitazone (10-100 µM) on the resting tension of isolated tracheal muscle of guinea pig. Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

centrations of histamine were studied on isolated tracheal muscle of the guinea pig. Histamine produced concentration dependent contraction of the tracheal muscle. This group (histamine control group) was taken as the control against which all other groups were compared. Them the effect of pioglitazone and indomethacin on the histamine induced contractions was studied separately as well as together to understand the involvement of prostaglandins in the mechanism of relaxation produced by pioglitazone.

In a report, two case subjects showed that the symptoms related to asthma had remitted during treatment with pioglitazone. In one patient the pulmonary function tests showed improvement of forced vital capacity from and forced expiratory volume, one month after the start of treatment with pioglitazone. Another man with diabetes and asthma was started on 15 mg pioglitazone, he stopped wheezing and coughing. When pioglitazone was discontinued 6 months later because his level of HbA_{1c} had not de-

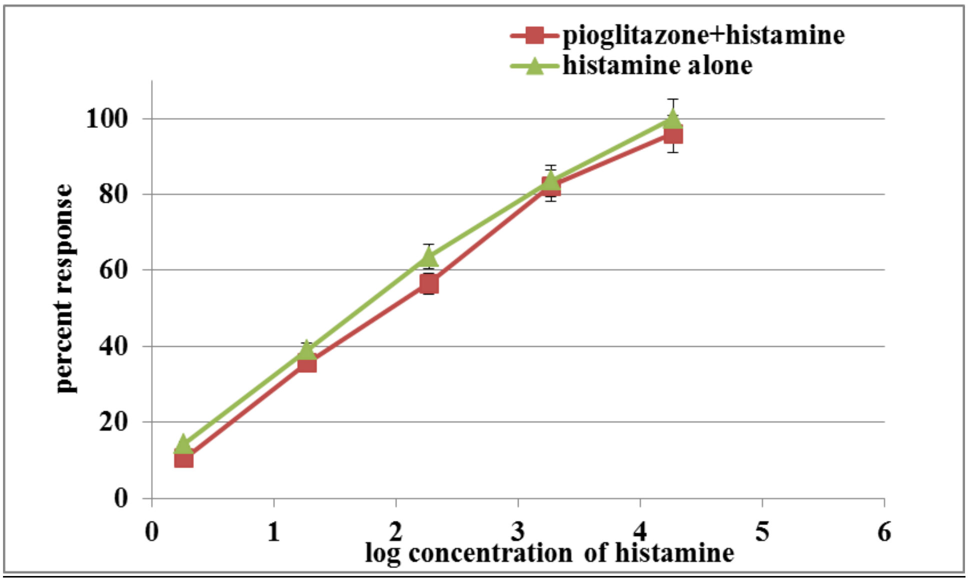

Figure 11. Log concentration response curve of group 1 (histamine control) and group 4 (histamine after pretreatment with pioglitazone). Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

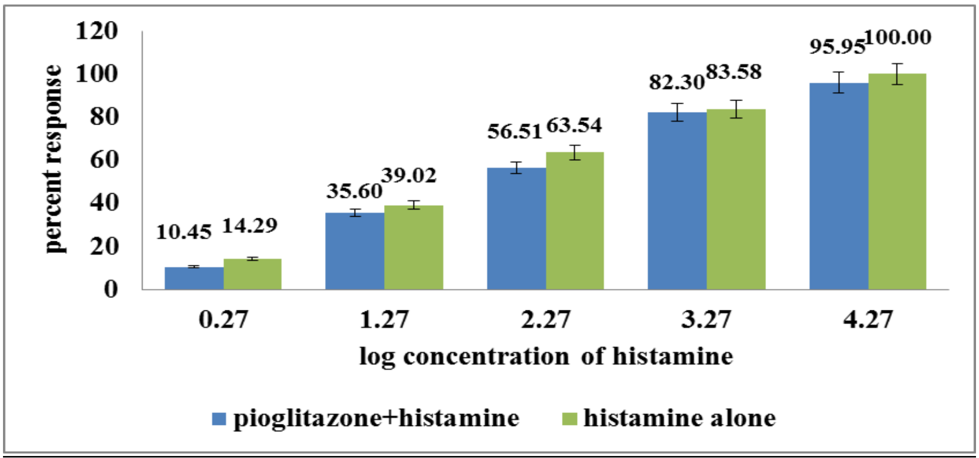

Figure 12. Bar diagram showing histamine induced contractions in group 1 (histamine control) and group 4 (histamine after pretreatment with pioglitazone). Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM).
* = Significant ($P < 0.05$)

creased significantly, his respiratory symptoms recurred. Based on the findings from two patients with diabetes and asthma, pioglitazone may ameliorate symptoms of asthma [21]. In another study conducted on 50 patients who were randomized into a control group receiving only standard therapy and a study group taking pioglitazone as part of combination therapy for 3 months, incorporation of pioglitazone improved the clinical course of asthma [22]. Keeping this in view, we compared the concentration response curve of histamine in isolated tracheal muscle pretreated with a fixed concentration of pioglitazone 100µM. Pioglitazone shifted the curve of histamine downwards and towards the right, with the percent response of 95.95 percent of the histamine control. The mean values of responses and mean percent responses when compared between histamine control group and pioglitazone pretreated group were found statistically significant ($P < 0.05$) at lower concentrations of histamine but insignificant at concentrations of 10^{-4} and 10^{-3} M. The mean percent deviation between these groups was 11.53 percent. So from these findings, we can conclude that pioglitazone decreases the histamine induced contractions of the tracheal muscle. Studies have shown pioglitazone to have relaxant effect on the tracheal smooth muscles [23]. Studies have also suggested the role of a PPAR-γ ligand, in the attenuation OVA-induced allergic inflammation in mice [24].

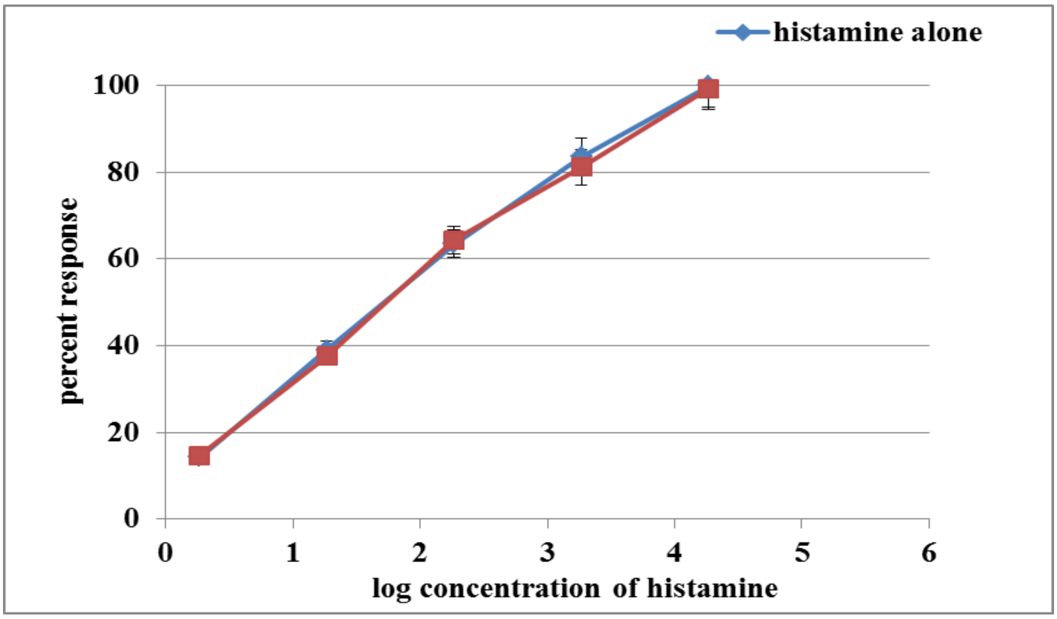

Figure 13. Log concentration response curve of group 1 (histamine control) and group 7 (histamine after pretreatment with indomethacin). Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

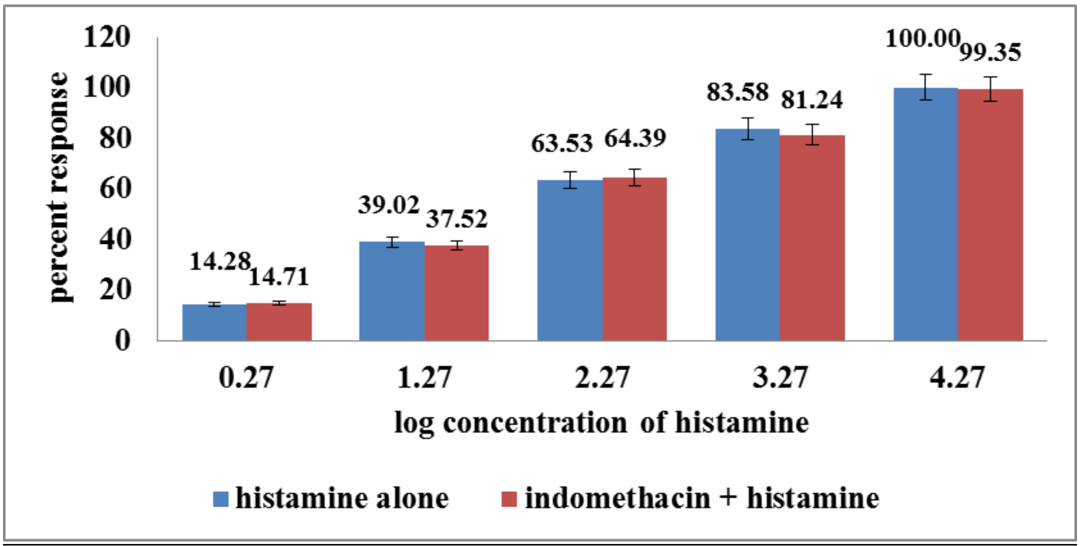

Figure 14. Bar diagram showing histamine induced contractions in group 1 (histamine control) and group 7 (histamine after pretreatment with indomethacin). Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM).
* = Significant ($P < 0.05$)

Our observations are further supported by a study which evaluated the effects of pioglitazone, in LPS-induced pulmonary dysfunction, inflammatory changes and oxidative stress in guinea pigs. Significant increase in the breathing frequency and bronchoconstriction accompanied with a significant decrease in tidal volume was seen after inhalation exposure to nebulized LPS and pioglitazone was found to be effective in abrogating the pulmonary dysfunction in this model of acute lung inflammation [25]. A study using OVA-induced murine model of asthma revealed that administration of PPARγ agonists reduces airway hyperresponsiveness which was showed by a shift to the right of the dose response curve of methacholine compared with that of untreated mice, indicating that rosiglitazone and pioglitazone treatment reduces OVA-induced airway hyperresponsiveness [26]. Results from a study comparing pioglitazone and dexamethasone after CRA challenge in a murine model of asthma indicated that the effectiveness of pioglitazone is similar to that of glucocorticoids [27]. A study investigating the effects of simvastatin and pioglitazone on airway inflammation and remodeling in a murine model of chronic asthma concluded that pioglitazone is relatively more beneficial in

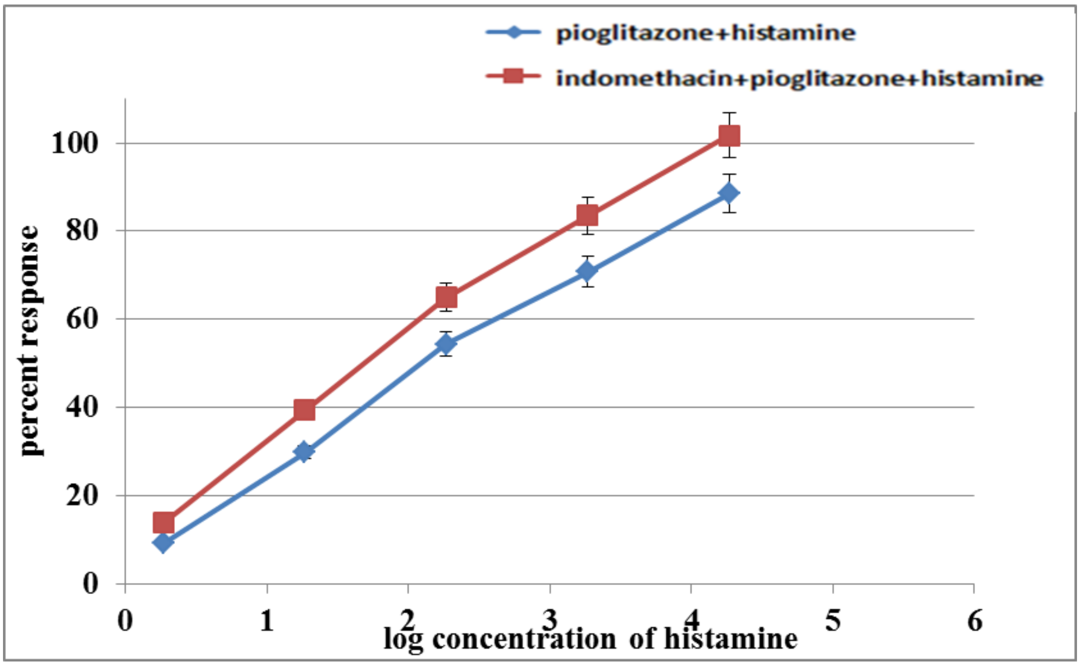

Figure 15. Log concentration response curve of group 3 (histamine after pretreatment with pioglitazone) and group 8 (histamine after pretreatment with indomethacin and pioglitazone). Results are average of six separate experiments for each group. Data are reported as mean ± standard error of the mean (SEM)

ameliorating airway wall remodeling in this murine model of chronic asthma than simvastatin [28].

Studies have revealed that PPARγ reduces airway hyper-responsiveness and activation of eosinophils through the modulation of prostaglandins [29]. The involvement of both the constrictor and relaxant prostaglandins in the effect of pioglitazone on airway smooth muscle was also evaluated and a set of experiments was designed for that purpose. The tracheal muscle was pretreated with indomethacin, a prostaglandin synthesis inhibitor and pioglitazone. The concentration response curve was then constructed using different concentrations of histamine. The concentration response curve and its parameters were compared with the concentration response curve obtained with histamine in tracheal muscle pretreated with pioglitazone alone. The mean values of responses as well as the mean percent responses when compared between the two groups were found statistically significant ($P < 0.05$) with the maximum amplitude increasing from 69.17±0.91 in pioglitazone pretreated group to 77.67±0.49 mm in indomethacin and pioglitazone pretreated group. The mean percent deviation was 24.08 percent. Indomethacin alone did not have any significant difference from histamine.

Studies have shown that bronchoconstriction in airway diseases may result from inflammatory mediators released by allergic reactions. The prostaglandins of the E series have been shown to mediate inhibition of the respiratory smooth muscle in rabbit, guinea pig, sheep and pig and it has been suggested that PGEs play an important role in maintaining bronchial tone in asthmatic patients [30]. In response to activation of protease-activated receptor 2 (PAR-2), prostaglandin E2 (PGE2) is generated by the airways [31]. Thiazolidinediones increase the level of PGE2 by inhibiting of 15-hydroxyprostaglandin dehydrogenase which is responsible for oxidation of PGE2 [32]. It has also been demonstrated that drugs which inhibit the cyclooxygenase pathway of arachidonic acid metabolism can reduce the effect of a relaxant prostaglandin such as PGE_2 [33]. Thus the involvement of relaxant prostaglandins in the broncho-relaxaing effect of the thiazolidinediones could be a possibility based on our study.

CONCLUSION

Pioglitazone produced a significant decrease on the histamine induced contractions as well as on the baseline resting tension of isolated tracheal smooth muscle of guinea pig, identifying its relaxant role on the smooth muscle through action on the PPAR gamma receptor. Prostaglandins also have an identifiable role in the effect of TZDs on isolated tracheal smooth muscle. This hypothesis was strengthened by the decrease in the relaxant effect of pioglitazone when used concomitantly with a prostaglandin inhibitor, indomethacin. It can therefore be concluded that Pioglitazone possess a relaxant effect on the tracheal smooth muscles not only through PPAR gamma receptor activation but in addition through the stimulation of prostaglandins.

Recommendations

Further exploratory work is recommended to elucidate the exact mechanism underlying the relaxing effect of thiazolidinediones in the isolated tracheal smooth muscle of guinea pig. Similar type of work may be carried out in a clinical study on the human volunteers having COPD. Studies are needed to verify the impact of regularly scheduled pioglitazone administration on spirometry, dyspnea, exercise capacity and improvement in quality of life.

Ethical committee code

Approved under registration code 2009-NUST-MPhil PhD-Med-10

CONFLICTS OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article

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