Original Article

The bronchodilatory effect of Propofol against Bradykinin induced contraction on guinea pig trachea

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Objectives: To study the protective effects of propofol against bronchoconstriction produced by bradykinin.

Methodology: Guinea pig trachea was first dissected and cut into 2-3mm wide rings. The trachea was then placed in Krebs Henseleit solution. The tracheal muscle activity was recorded by Research Grade Isometric Force Transducer DT-475 (USA) on power lab data acquisition unit. Effect of increasing concentration of Acetylcholine and bradykinin were recorded and cumulative dose response curves were plotted. Acetylcholine was taken for comparison purposes and its response was considered to be 100 percent. Propofol was then added in fixed concentration to study its effect on tracheal muscle.

Results: Acetylcholine and bradykinin produced reversible contraction at maximum mean±SEM of 0.015±0.0006 mV and 0.014±0.0007 mV. Propofol showed relaxation of the guinea pig tracheal muscle in a fixed dose of 22 μM at a maximum mean±SEM value of 0.006±0.0004 mV producing a maximum response of 38 percent and shifting the dose response curve to the right and downwards.

Conclusion: Propofol significantly ameliorated the bronchoconstriction produced by bradykinin showing that the mechanism of tracheal relaxation in asthmatic individuals can be through the inhibition of bradykinin mediator. (Rawal Med J 201;42:235-238)

Keywords: Bradykinin, propofol, trachea, bronchodilation.

INTRODUCTION

Asthma is one of those major health problems whose prevalence is continuously increasing with the passage of time.[1] In asthmatic individuals, the level of kinins are found to be increased in the bronchoalveolar lavage fluid after an allergen challenge.[2] A major feature of asthmatic airways is airway hyper reactivity and studies have shown kinin receptor upregulation mainly B_1 and B_2, to play a key role in the production of this hyper reactivity.[3] Bradykinin is a potent inflammatory mediator that produces characteristic features of inflammation. The response of bradykinin administered through various routes varies in different species.[4] In asthmatic individuals, inhaled bradykinin produces a very potent bronchoconstrictor effect.[5] The constriction and relaxation response produced in guinea pigs depend on the presence and absence of tracheal epithelium. In vitro studies on denuded guinea pig trachea demonstrates bronchoconstriction.[4] One of the studies suggests that the mechanism behind this bradykinin induced smooth muscle contraction is prostanoid production and intracellular release of calcium.[6]

During induction of anesthesia, in patients with hyper reactive airway diseases like asthma, there is risk of intense bronchospasm. Among the intravenous anesthetics, Propofol is the most commonly used.[7] It is an ultra-short acting agent which is known for its sedative and amnestic properties.[8] Its bronchodilatory effect on the airways is already known and different studies have demonstrated different mechanisms underlying this effect.[9] Some studies suggest that caveolae disruption and decrease in the intracellular calcium

concentration is the possible mechanism involved in relaxation of airways.[10] Others suggest role of tachykinins in this aspect.[11] Some studies have shown the protective effect of propofol against vagal and methacholine induced contraction mainly by its direct muscarinic action.[12] But no study has yet been done to find out the whether propofol ameliorates the bronchoconstriction induced by bradykinin. This study was performed to assess the protective effects of propofol against bronchoconstriction produced by bradykinin in guinea pigs.

METHODOLOGY

It is a laboratory based randomized control trial that was conducted in the Department of Pharmacology & Therapeutics in collaboration with the Department of Physiology. Experiments were carried out using eighteen adult healthy guinea pigs both male and female of Dunkin Hartley variety. The guinea pigs were randomly divided into 3 groups with six animals in each group. Study protocol was approved by Ethics Committee of Centre for Research in Experimental and Applied Medicine (CREAM), Army Medical College, Rawalpindi.

The guinea pigs were first killed by cervical dislocation.[13] The whole of the trachea was dissected, epithelium was removed by simple rubbing[14] and was cut into 2-3 mm wide rings. The tissue was then transferred to the organ bath of 50 mL capacity containing Krebs solution at 37?C, aerated with oxygen continuously.[15] One end of the trachea was attached to the oxygen tube in the organ bath and the other end was connected to research grade Isometric Force Transducer DT-475 (USA). The tissue was allowed to rest for an equilibrium period of 15 minutes after which the tracheal muscle activity was recorded on power lab data acquisition unit (AHK/214 iworx).

Group I cumulative concentration response curve of Acetylcholine: The cumulative dose response curve was plotted using acetylcholine (Ach) in concentration ranging from 10^{-3} to 10^{-6} M. When the maximum effect was produced in the concentration of 10^{-3} M, then subsequent doses 3, 6, 9, 12, 15 and 18 µg were added cumulatively. Ach served as a control group and the response produced by it was taken to be 100 percent, to compare it with the bradykinin induced contraction.

Group II cumulative concentration response curve of bradykinin: The dose response curve was produced by bradykinin in a maximum concentration of 10^{-4} M with increasing doses of 11, 22, 33, 44, 55 and 66 µg.

Group III cumulative concentration response curve of bradykinin with fixed dose of propofol: The concentration response curve with bradykinin was plotted by using fixed dose 22 µM of propofol.

Data analysis was performed using SPSS version 22. To find significant difference between two groups student's t-test was applied.

RESULTS

Acetylcholine and bradykinin produced dose dependent contraction of the tracheal tissue with maximum amplitude of contraction and percent values of 0.015±0.0006 mV, 0.014±0.0007 mV and 100 percent and 96 percent, respectively. The tracheal muscle pretreated with propofol produced the maximum amplitude of contraction of 0.006±0.0004 mV giving a maximum percent response of 38 percent. The response curve was shifted towards right and downwards by propofol, showing significant change in the bronchoconstriction induced by bradykinin (Fig. 1)

Figure 1: Cumulative dose response durve of bradykinin in the presence of fixed dkose (22 uM) of propofol plotted on power lab using tracheal chains of guinea pig (n=6) showing a contraction of less amplitude.

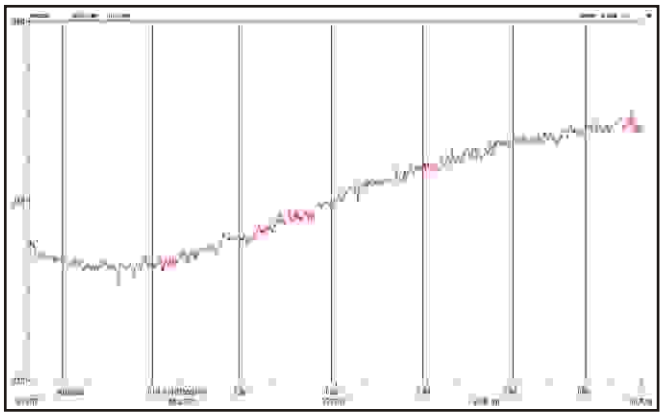
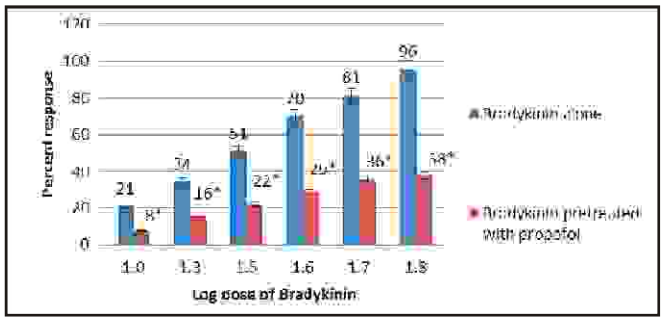


Figure 2: Bar diagram demonstrating the comparison between group II showing bradykinin induced contraction of tracheal muscle and group III showing the contraction after pretreatment with propofol on tracheal muscle of guinea pig (n=6). The results are expressed as Mean±SEM.



***(mean p=0.001) =Significant (p<0.05)**

The comparison of mean value of contraction and percent of responses between group II and III was found to be statistically significant (p< 0.05). The percent inhibition for group II and III was also calculated to be 63 percent, 55 percent, 57 percent, 59 percent, 56 percent and 60 percent, respectively (Fig. 2).

DISCUSSION

The current study was carried out to evaluate the effect of propofol against the bradykinin induced bronchoconstriction in guinea pig trachea in vitro and to explore one possible mechanism by which propofol causes relaxation in asthmatic patients. Acetylcholine and bradykinin showed a dose dependent reversible contraction of tracheal rings. Ach was used in a concentration ranging from 10^{-6} to 10^{-3} M, which is similar to the study by Kim et al in which the relaxant effect by propofol and ketamine was shown to be produced against Ach induced contraction.[16] Doses of bradykinin ranging from 11 to 66 µg also produced significant contraction of the guinea pig denuded tracheal smooth muscles, which were consistent with the findings in a study in which the bradykinin produced contraction in a dose starting from 11 µg but maximum contraction was produced at a dose of 77 µg.[17] Maximum percent response produced by bradykinin was 96 percent.

The tracheal smooth muscle pretreated with fixed dose of propofol 22 µg demonstrated significant relaxation with bradykinin induced contraction. The dose response curve shifted towards the right with a maximum percent response of 38 percent. These findings were similar to a study which showed that at a dose of 20 µg propofol inhibited Ach, neurokinin and substance P induced contraction.[11] Another study suggested the direct relaxant effect of propofol with $CaCl_2$ induced contraction through the inhibition of calcium channels.[18]

The comparison between bradykinin alone and propofol pretreated groups showed maximum percent inhibition of 63 percent. The percent responses between the two groups were found to be statistically significant (p<0.05). This study provides the first evidence that propofol has protective effect against bradykinin induced bronchoconstriction, thus emphasizing on its role in asthmatic patients undergoing induction. Further evaluation regarding the mechanism of this bronchodilatory action can be done.

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CONCLUSION

Propofol significantly ameliorated the contractile response of bradykinin on bronchial smooth muscles showing that one of the protective responses of propofol in asthmatic individuals is through inhibition of bradykinin. Clinical trials regarding relation with human airway smooth muscle can further be carried out.

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