PRELIMINARY COMMUNICATIONS

Antagonistic Action of Aerosols of Prostaglandins $F_2\alpha$ and E_2 on Bronchial Muscle Tone in Man

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British Medical Journal, 1972, 3, 212-213

Summary

Experiments were carried out in healthy male volunteers to investigate the effect of the inhalation of prostaglandin $F_2\alpha$ ($PGF_2\alpha$) on airways resistance and the influence of the subsequent inhalation of prostaglandin E_2 (PGE_2). Airways resistance, which reflects the tone of smooth muscle in the larger airways in man, was measured by total body plethysmography.

The inhalation of $PGF_2\alpha$ (40-60 μg) caused an increase in airways resistance in all subjects. Both PGE_2 (55 μg) and isoprenaline (550 μg) given by metered aerosol promptly reversed the bronchoconstriction induced by $PGF_2\alpha$, but isoprenaline was more effective in this respect.

A role for these prostaglandins in the control of bronchial muscle tone is discussed.

Introduction

Prostaglandins affect human bronchial muscle in different ways depending on their structure and route of administration. Those of the E series relax bronchial muscle, and both prostaglandins E_1 and E_2 (PGE_1 and PGE_2) cause bronchodilation in asthmatic subjects when given by metered aerosol (Cuthbert, 1969, 1971). On the other hand, those of the F series, and particularly prostaglandin $F_2\alpha$ ($PGF_2\alpha$), are bronchoconstrictor in action. On isolated human bronchial muscle PGE_1 and $PGF_2\alpha$ cause relaxation and contraction respectively and each tend to reduce or modify the effect of the other (Sweatman and Collier, 1968).

By measuring airways resistance, which reflects changes in the tone of smooth muscle in the larger airways in man, we have recently investigated the effect of inhaled $PGF_2\alpha$ and the influence of the subsequent inhalation of PGE_2 or isoprenaline.

Present Study

Experiments were carried out on four healthy male volunteers aged between 26 and 41 years. The subjects' intelligence and training were such that they could appreciate the nature of the experiments. Each subject inhaled an aerosol of $PGF_2\alpha$ (as tromethamine salt) generated from a 500 $\mu g/ml$

solution, from a pressure cycled ventilator (Bennett) adjusted to nebulize on inspiration only. By weighing the nebulizer, its connexions, and mouthpiece before and after inhalation it was possible to estimate the quantity of drug delivered to the subject, although the precise amount deposited in the bronchi was uncertain. Each subject took 10 maximal inspirations from this apparatus and the amount of $PGF_2\alpha$ delivered was 40-60 μg . Immediately after the inhalation the subject entered a constant-pressure body plethysmograph, and measurements of airways resistance and lung volume were obtained at predetermined intervals by the method of Dubois, Botelho, and Comroe (1956). As airways resistance (R_{aw}) varies with lung volume the results were expressed as changes in specific airway conductance (SG_{aw}) according to the relation: $SG_{aw} = 1/R_{aw}/\text{Lung Volume}$ (1./cm H_2O/sec).

At least five readings of SG_{aw} were obtained at each time interval in each subject and the mean value was calculated, the series of readings taking about five minutes to complete. Thus readings of SG_{aw} were obtained 3-7, 10-14, 15-19, 30-34, and 52-58 minutes after inhalation of $PGF_2\alpha$. The reading to reading variation in the method was small; on no occasion did the standard deviation of the mean of any group of readings exceed ± 0.01 1./cm H_2O/sec . The immediate effect of the inhalation of $PGF_2\alpha$ was pharyngeal irritation and coughing which lasted 5-10 minutes. After a short latent period, two examples of which are shown in Fig. 1, there was a decrease in SG_{aw} in all four subjects. The maximum change in these two factors usually occurred within four to six minutes and there was a subsequent return to normal within 30-40 minutes of the inhalation. Wheezing or shortness of breath did not occur. The bronchoconstrictor

FIG. 1—Record of changes (absolute values) in specific airway conductance (SG_{aw}) after inhalation of prostaglandin $F_2\alpha$ in two healthy male subjects. Note delay between inhalation and onset of bronchoconstriction.

response to the inhalation of $PGF_2\alpha$ in each subject having been established the experiment was repeated, but immediately after the fall of SG_{aw} had occurred PGE_2 55 μg (as triethanolamine salt) was given by metered aerosol. Finally, a third experiment was performed on each subject in which isoprenaline sulphate 550 μg was given in the same manner. Metered doses of PGE_2 and isoprenaline consisted of 110 μl (two valve actuations) of the active principle dissolved in ethyl alcohol and fluorinated hydrocarbon propellants.

The inhalation of $PGF_2\alpha$ resulted in a highly reproducible fall in SG_{aw} (mean fall 0.0292 1./cm H_2O/sec , $P < 0.001$,

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Student's *t* test). The inhalation of PGE_2 significantly reversed the broncho-constriction at 10-14 minutes after $\text{PGF}_{2\alpha}$ ($P < 0.05$), but thereafter the rate of recovery did not differ from

FIG. 2—Record of mean changes in specific airway conductance (SGaw) $\pm$ S.E. of mean after inhalation of prostaglandin $\text{F}_{2\alpha}$ in four healthy male subjects. Broken line indicates effect of inhaling 55 μg PGE_2 8 minutes after inhalation of $\text{PGF}_{2\alpha}$.

FIG. 3—Procedure as in Fig. 2 except that at minute 8 isoprenaline 550 μg was given by metered aerosol to each subject.

that of $\text{PGF}_{2\alpha}$ alone (Fig. 2). On the other hand isoprenaline caused a prompt and complete reversal, and in some subjects the SGaw increased beyond the control levels (Fig. 3). This difference might be explained by the larger dose of isoprena-

line, but a previous study (see below) had shown that in these doses PGE_2 and isoprenaline are approximately equipotent bronchodilators. Bronchoconstriction after the inhalation of $\text{PGF}_{2\alpha}$ could have been due to its primary irritant effect. However, the latent period between the inhalation and the onset of bronchoconstriction is unlike the response to irritants which usually occurs immediately after inhalation (Nadel and Comroe, 1961; Sterling, 1967), nor is the bronchoconstriction of $\text{PGF}_{2\alpha}$ influenced by earlier inhalation of atropine methonitrate (to be published), although atropine reduces the response to inhaled irritants (Widdicombe *et al.*, 1962; Sterling, 1967).

Comment

Prostaglandins E_2 and $\text{F}_{2\alpha}$ are normally present in the human lung and bronchi (Änggård, 1965; Karim *et al.*, 1967), and the finding that they have mutually antagonistic actions in vitro (Sweatman and Collier, 1968) and in healthy human subjects suggests a physiological role for these substances in the control of bronchial muscle tone. In our experience PGE_2 (55 μg) and isoprenaline (550 μg) have approximately equivalent bronchodilator properties in both normal and asthmatic subjects (to be published). The present results show that in these doses isoprenaline is consistently more effective in reversing $\text{PGF}_{2\alpha}$ -induced bronchoconstriction in healthy subjects. This suggests that normal bronchial muscle tone and bronchoconstriction in asthma differ in some fundamental way from $\text{PGF}_{2\alpha}$ -induced bronchoconstriction. Moreover, the delay encountered in the onset of the bronchoconstrictor action of $\text{PGF}_{2\alpha}$ suggests that this prostaglandin may itself be releasing another bronchoconstrictor agent or possibly undergoing metabolism to a more active form.

Experiments are in progress by which it is hoped to clarify the relation between the prostaglandins and the control of bronchial muscle tone.

We are indebted to Dr. A. Knell and Dr. C. Roberts for agreeing to take part in this study, and to Dr. R. Jacomb, of Upjohn Ltd., for supplies of $\text{PGF}_{2\alpha}$ and Dr. D. R. Maxwell, of May & Baker Ltd., for the PGE_2 and isoprenaline aerosols.

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