Tolerance to sympathomimetic bronchodilators in the guinea pig lungs

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Between 1959 and 1966, in England and Wales an increase in asthma mortality rate was noted which was related to the use of pressurized aerosols containing sympathomimetic bronchodilators. Several suggestions were proposed to explain why pressurized aerosols caused an increase in asthma deaths and these include:

1. Irritation of the respiratory tract exacerbating the asthmatic attack.
2. Pulmonary vasodilator effect of some bronchodilator drugs leading to reduced arterial oxygen tension.
3. Sensitization of the heart to sympathomimetic amines by the propellants of the aerosol.
4. Cardiac stimulatory effect.

Objections have been raised to all these postulates, but more recently Conolly, Davis, Dollery & George (1971) suggested that excessive use of sympathomimetic amines by patients may produce a state of drug-induced cross-resistance to endogenous sympathetic stimulation in the respiratory tract which might lead to a deterioration in asthmatic state.

A simple isolated tissue technique perfusing the bronchial tree through the trachia as described by Tainter, Pedden & James (1934) was utilized to investigate this hypothesis in the guinea pig. A flow recorder was used to determine the rate of perfusion. Pretreatment of the animals subcutaneously three times daily with adrenaline (5 μg/kg) reduced the response of the isolated perfused histamine constricted lungs of the animal when it was challenged with adrenaline (Figure 1). A similar effect was observed when the guinea pigs were pretreated with isoprenaline or adrenaline and challenged with either the same or a different sympathomimetic bronchodilator. The longer the animals were pretreated and the higher the dose of bronchodilator, the greater was the degree of tolerance developed.

Similarly, tolerance developed to aminophylline following pretreatment with aminophylline or isoprenaline, and cross tolerance developed to adrenaline following pretreatment with aminophylline.

These results suggest that asthmatic patients who use bronchodilators excessively may become refractory to these drugs, and support the hypothesis that induced cross-resistance to endogenous sympathetic stimulation could lead to a deterioration in the asthmatic state of these patients.

Reference

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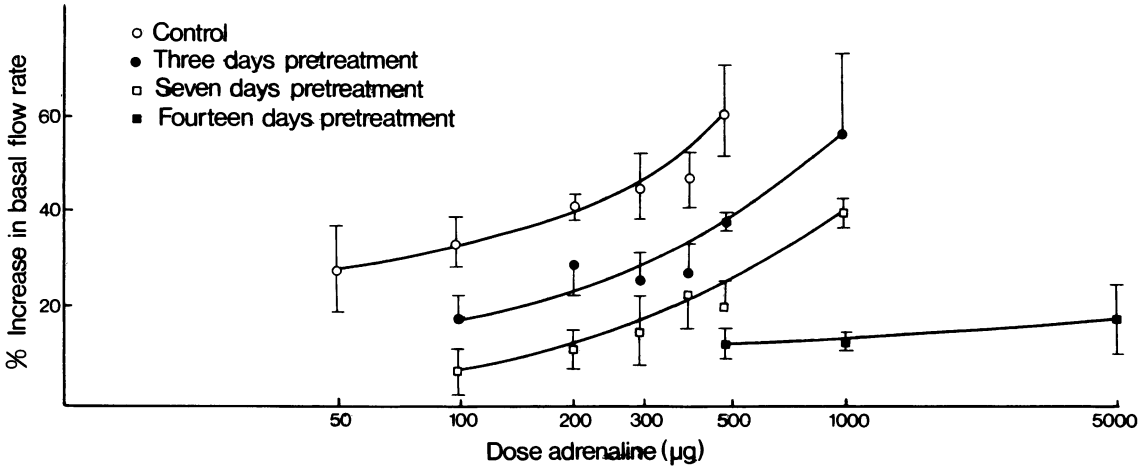

Figure 1 The effect of pre-treatment with 5 μg/kg adrenaline on the response of the guinea-pig isolated perfused histamine-constricted lungs to adrenaline.