of ≥ 15 IU/ml the fetus could be severely anaemic and therefore cordocentesis should be considered.

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Inhaled atrial natriuretic peptide and asthmatic airways

Geoffrey Hulks, Neil C Thomson

Department of Respiratory Medicine, Western Infirmary, Glasgow G11 6NT
Geoffrey Hulks, Wellcome Research Fellow
Neil C Thomson, consultant physician

Correspondence to:
Dr G Hulks, Department of Respiratory Medicine, City Hospital, Edinburgh EH10 5SB.

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Pathophysiological plasma concentrations of atrial natriuretic peptide have been shown to have a bronchodilator effect in constricted asthmatic airways,^{1,2} and lower doses may decrease bronchial hyper-responsiveness,³ a hallmark of asthma. This observation is of considerable interest as animal models suggest that the intracellular action of atrial natriuretic peptide in the airway is mediated by cyclic GMP,⁴ whereas β agonists, which are the current first line bronchodilator treatment for asthma, act through cyclic AMP.

Drugs for treating airway diseases are best given directly into the airway itself, and the purpose of this study was to ascertain any bronchoprotective effect of inhaled atrial natriuretic peptide.

Subjects, methods, and results

We studied eight subjects (three women) with atopic asthma. Their mean forced expiratory volume in one second (FEV_1) was 94% (SD 8%) of the predicted value. All subjects showed at least moderate bronchial hyperreactivity to inhaled histamine—that is, histamine at a concentration of ≤ 2 mg/ml, produced $\geq 20\%$ fall in FEV_1 .

On three separate days subjects received either nebulised atrial natriuretic peptide (0.1 mg or 1 mg) or placebo in a double blind, randomised manner. FEV_1 was tested at 30, 90, and 180 seconds after inhalation and immediately thereafter a single two minute inhalation of histamine was given in a dose extrapolated from the screening visit to produce a 25% fall in FEV_1 . FEV_1 was measured again at 30, 90, and 180 seconds and repeated at 5, 10, 15, and 20 minutes.

Forced expiratory volumes at baseline and after atrial natriuretic peptide were compared by analysis of variance.

There was no significant variation in baseline FEV_1 between study days nor was there any significant change in FEV_1 after atrial natriuretic peptide alone. All subjects showed a pronounced inhibition of histamine induced bronchospasm with 1 mg atrial natriuretic peptide (figure). The maximum fall in FEV_1 was 26.8 (SE 0.7)% with placebo, 22.6 (3.3)% with 0.1 mg atrial natriuretic peptide, and 9.2 (2.2)% with 1 mg ($p < 0.001$, placebo v 1 mg atrial natriuretic peptide). No side effects were reported or observed.

Comment

This is the first report that atrial natriuretic peptide effectively protects the hyperreactive airway when given by inhalation. The observation is of particular interest as atrial natriuretic peptide is believed to work by a linkage of guanyl cyclase and the generation of cyclic GMP⁴ and thus represents a different intracellular mechanism to β agonists, for which the

Mean (SE) change in forced expiratory volume in one second in response to inhaled histamine after pretreatment with inhaled atrial natriuretic peptide in eight asthmatic subjects

generation of cyclic AMP is linked to adenylyl cyclase.

We assume that atrial natriuretic peptide achieves its effect by acting directly on smooth muscle in the airway. In support of this, animal models have shown that atrial natriuretic peptide in tracheal preparations has a direct, dose dependent, relaxant effect.^{4,5} Atrial natriuretic peptide has been localised by autoradiography to smooth muscle in rat bronchi and bronchioles, but a receptor population in the human airway has not been directly sought. It should be emphasised that other possibilities remain to account for the observed effect. Atrial natriuretic peptide has been shown to exert some of its renal effects by altering mucosal ion transport, and similar effects in airway smooth muscle might affect airway reactivity. Atrial natriuretic peptide can modulate vagal activity and ganglionic neurotransmission and, although this evidence pertains to vascular models, similar actions in the airway could be relevant.

We have shown that a substance believed to act by a different intracellular mechanism to current first line bronchodilator treatment for asthma has a significant bronchoprotective effect when given by inhalation. We therefore suggest that natural or synthetic compounds that work by a similar mechanism warrant further investigation as potential therapeutic agents to be given by this route.

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