Benha M. J.
Vol. 15 No 3 Sept. 1998

ATRIAL NATRIURETIC PEPTIDE IN BRONCHIAL ASTHMA IN CHILDREN

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Abstract

The hormone atrial natriuretic peptide (ANP) causes bronchodilatation and partially protects against direct and indirect bronchial challenges in patients with asthma. The present study was carried out to determine the role of ANP in bronchial asthma in children. Twenty asthmatic children with age ranged from 1.5 to 11 years old were subjected to clinical, laboratory and radiological studies. Plasma ANP has been measured for the asthmatic group during acute sever asthma and at least 4 weeks later while clinically stable, as well as, for a control group who included 15 clinically free children with appropriate age and sex. The mean plasma value of ANP during acute sever asthma (9.25±2.95 pg/ml) was significantly higher (P<0.001) than the corresponding values of clinically stable asthmatic children (6.13±2.72 pg/ml) and the-control group (1.45±1.12 pg/ml). Also, the difference between the mean plasma ANP values of clinically stable asthmatic children and the control group was statistically highly significant (P<0.001). We concluded that ANP could be considered one of the mediators of asthma modulation that increased in asthmatic children to protect against bronchoconstriction.

Introduction and Aim of the Work

Atrial natriuretic peptide (ANP) is a 28 amino acid hormone secreted by the cardiac muscles mainly in the right atrium and in the lung it is secreted by type II pneumocytes and respiratory epithelial cells. It has natriuretic, diuretic and vasodilator properties (Di-Nardo et al, 1992). The lung contributes only to a small extent

to the production of circulating ANP, on the other hand, the lung represents tlle major degrading site of this protein (Di-Nardo et al, 1996). Plasma ANP concentration increment during lung disease may therefore be due to a reduction in ANP plasma removing enzyme (neutral endopeptidase) rather than to increase ANP production (Fluge et al, 1995). ANP induces cGMP mediated relaxation of bronchial smooth muscles. It has a bronchodilator action in patients with asthma and has been shown to protect against histamin-induced bronchoconstriction (Chanez et al, 1992). Moreover, ANP determines pulmonary artery vasodilatation, thus contributing to improved pulmonary circulation. Also ANP at physiological levels may prevent pulmonary edema by increasing cGMP, decreasing intracellular Ca^{+2} and stabilizing tight junctions (Di-Nardo et al, 1996). Although the role of ANP in lung diseases in adults was researched in last few years, yet its role in pediatric age is not well studied. The present study aimed to assess plasma ANP levels during acute sever asthma in children and in between attacks, and comparing them with a healthy control group, in order to establish its role in the pathogenesis of asthma in children.

Subjects and Methods

The present study was carried out on 20 asthmatic children with age ranged from 1.5 to 11 years old and of both sexes. They were admitted in the Pediatric Department of Benha University Hospital due to acute sever asthma.

All asthmatic children were subjected to detailed history, thorough clinical examination, complete blood picture, and chest X-ray in order to diagnose asthma. They met the criteria of asthma definition provided by the International Consensus Report (1992). We excluded patients with other clinical disorders rather than asthma. Blood samples were drawn from all children at the same time of the day to measure ANP plasma levels during acute state. At least 4 weeks later another blood samples were drawn from the previous asthmatic group while clinically stable i. e. inbetween attacks.

15 children who were clinically free (not asthmatic) with appropriate age and sex were included in our study, as a control group, and blood samples were drawn from them to measure plasma ANP values for comparison.

Blood samples were placed into EDTA tubes, plasma was rapidly separated, stored at -70°C until measured. Measurement was done by a specific and sensitive Competitive Enzyme Immunoassay. Kit was purchased from Peninsula Laboratories Inc. ANP was extracted from plasma using C_{18} Sep columns and eluted with a mixture of acetonitrite and trifluoroacetic acid. The lower limit of detection for the assay was 0.1 pg/ml (Porstmann and Kiessig, 1992).

Results

The mean value of plasma ANP in children with acute sever asthma was 9.25 ± 2.95 pg/ml, while that of the control group was 1.45 ± 1.12 pg/ml. The difference between the two groups was statistically highly significant ($p<0.001$) (Table I & Fig 1).

The mean plasma value of ANP in asthmatic children in between attacks was 6.13±2.72 pg/ml, it was significantly lower ($p<0.001$) than that of acute sever asthma, but significantly higher ($p<0.001$) than that of the control (Table I & Fig 1). Statistical analysis of our results was performed by using paired t test.

Table 1 : Plasma ANP levels during acute sever asthma and in between attacks in comparison with a control group .

ANP (pg/ml) / Different groups	X	± SD	Test of Significance		
			Between	t	p
During acute asthma	9.25	2.95	Acute asthma vs in-between attacks.	3.48	<0.001
In-between attacks	6.13	2.72	Acute asthma vs control	10.83	<0.001
Control group	1.45	1.12	In-between attacks. vs control	6.95	<0.001

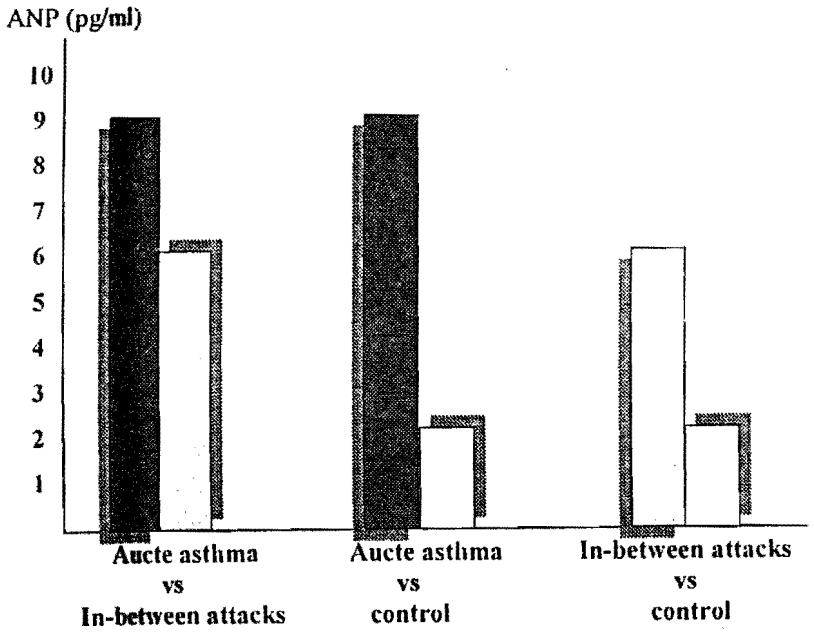

Fig. 1 : Plasma ANP levels during acute sever asthma and in between attacks in comparison with a control group.

Discussion

Atrial natriuretic peptide (ANP), a peptide involved in the regulation of circulatory homeostasis and bronchodilatation, is produced by myocardium, lung and several other tissues (Di-Nardo et al, 1996). Although the lung contribution to circulating ANP concentration is modest, its capacity of degrading ANP is very high, the lung being one of the major sites of ANP catabolism (Chanez et al, 1992). In particular, the ANP production pattern in the respiratory system and its functional relevance remains to be not well defined.

The increased mean values of plasma ANP in our cases of acute sever asthma has been previously reported by Di-Nardo et al (1992), Fluge et al (1995), and de -Gouw et al (1996). This increment has been also reported in other chronic obstructive lung diseases like emphysema and chronic bronchitis, particularly during exacerbation (Skwarski et al, 1993) .

Similar to our results were those of Hulks et al (1991), Menard (1991), and of Almirall & Hedenstierna (1991), who said that ANP has been proposed to participate in the pathogenesis of asthma, and it has been found to have a bronchodilatory effect on asthmatic patients. This bronchodilator effect is cGMP- mediated and it is considered a protective mechanism against bronchoconstriction. Scharf et al (1989), also postulated that acute asthma causes a fall in inspiratory pleural pressure, with bronchoconstriction eliciting a marked increase in functional residual capacity. This results in a higher negative force surrounding the atria at inspiration, augmenting right atrial distension and contributing to ANP release. Another mechanisms include increase in airway resistance which increase alveolar pressure and rise pulmonary vascular resistance (Adnot et al, 1987), as well as, activation of sympathetic nervous system and increase in heart rate which occur in acute sever asthma (Scliiebinger and linden, 1986), with a corresponding increase of atrial contraction that stimulate specific granules for ANP release. Recent studies (Di-Nardo et al, 1996) confirms the enhancelnent of ANP receptor gene expression and localization in the respiratory system induced by hypoxia during acute state.

Di-Nardo et al (1992), demonstrated that plasma ANP increment during lung disease could be due to a reduction in ANP plasma removal enzyme rather than to increased ANP production. Neutral endopeptidase (NEP) is one of the main enzmes for the clearance of ANP and it is found in the lung (Scliebinger and linden 1986). Many authors studied the effect of neutral endopeptidase (NEP) inhibitor (e.g. thiorphan) by inhalation or infusion on asthmatic patients and the results were increased ANP plasma level and bronchodilator response (Slciebinger and linden 1986; Angus et al 1996; and Nully et al 1994).

In the present study, the mean value of plasma ANP in our asthmatic children in between attacks, inspite of being significantly higher than the control healthy group, but still significtly lower than that of acute sever asthma. Similar