

Acute asthma and antidiuretic hormone secretion

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ABSTRACT Plasma antidiuretic hormone concentrations were measured in a group of children with acute asthma and in a control group. Very high levels of antidiuretic hormone were found in the asthmatic group. There were no changes in other biochemical indices. If overproduction of antidiuretic hormone is sustained then fluid administration to children with severe acute asthma is potentially dangerous.

In patients with acute asthma decreased filling of the left atrium occurs owing to increased resistance to blood flow through the pulmonary vascular bed. This in turn acts as a potent stimulus to the release of antidiuretic hormone.¹ The stimulus can be exacerbated by the additional infusion of intravenous salbutamol, which has a similar antidiuretic hormone-stimulating effect.²

Despite reports of raised antidiuretic hormone levels in status asthmaticus³ and of the syndrome of inappropriate secretion of antidiuretic hormone⁴ associated with acute asthma, many publications continue to advocate increasing fluid intake in the management of acute asthmatic episodes to combat dehydration.⁵ This paper presents the results of a controlled study of plasma antidiuretic hormone concentrations and urine and plasma osmolality in a group of children with acute asthma.

Methods

THE PATIENTS

We studied 10 children (five boys and five girls) with severe acute asthma aged from 1 year 2 months to 12 years (mean 6 years). A control group of 10 children was drawn from children who had no infectious, endocrine, or gastrointestinal disorder and were having a blood sample taken as part of their own investigations.

Each child in the control group had a full clinical examination carried out and a history obtained. No special precautions such as overnight fluid restrictions were placed on these children. Care was taken,

however, to ensure that there had been a normal fluid intake during the 12 hours before blood sampling.

The asthmatic children were included in the study if their attack of asthma was severe enough to merit intravenous treatment. After admission to hospital a full clinical examination was performed and a history obtained. Before treatment was started or any intravenous fluids administered blood samples were taken for determination of serum sodium, urea, and creatinine concentrations; plasma osmolality; plasma antidiuretic hormone concentration; and urinary osmolality. Similar samples were obtained from the control group.

All specimens were obtained while the child was sitting and only those patients who were normotensive at the time of examination were included. Spot urine specimens were obtained within five minutes of the time of blood sampling.

EXTRACTION AND ASSAY OF ANTIDIURETIC HORMONE

Samples for assay of antidiuretic hormone were collected on ice and centrifuged immediately at 4°C and the plasma was stored at -70°C until assay.

Antidiuretic hormone was extracted from plasma with octadecylsilyl-silica (Waters Associates, Massachusetts) as described by LaRochelle *et al.*,⁶ except that the hormone was recovered from silica with two 1-ml volumes of acetonitrile:water:acetic acid (75:25:4 v/v) and the pooled effluent blown to dryness at 37°C under a stream of air. Recovery of antidiuretic hormone added to plasma in the range 1-20 pmol/l (1-8.7 µU/ml) was 89% ± 4% (n = 12). Assayed antidiuretic hormone levels were not corrected for extraction loss.

Antidiuretic hormone antiserum was obtained from a chinchilla rabbit in response to immunisation

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with an antidiuretic hormone:bovine-thyroglobulin (40:1) conjugate. The antiserum had an affinity constant of 3.88×10^{11} /mol by Scatchard analysis and shows negligible cross-reaction with oxytocin ($< 0.0001\%$ w/w).

Radioimmunoassay for antidiuretic hormone was performed in a 0.05 mol/l tris/HCl buffer pH 7.4, containing 100 mg/dl bovine serum albumin. Reconstituted patient extract or synthetic antidiuretic hormone (AB Ferring, Sweden; 400 IU/mg), antidiuretic hormone antiserum (final dilution 1:170 000) and mono- (^{125}I) -antidiuretic hormone⁷ in a final volume of 0.5 ml were incubated for 72 hours at 4°C and bound and free hormone were then separated with donkey anti-rabbit gamma globulin (Wellcome, UK). At dose levels 1.1, 3.4, and 8.7 fmol (0.5, 1.5, and 3.8 μU) coefficients of variation were under 10% within assay (72 df in each case) and respectively 21%, 11%, and 13% between assays (7 df). The assay detection limit is 0.25 fmol at the 95% confidence level.

Results

No child was considered to be dehydrated at the time of the clinical examination on the grounds of skin turgor, weight loss, or mucous membrane changes. There were no abnormal changes in the serum urea or creatinine concentration. The mean concentrations of serum urea and creatinine in the asthmatic group were 4.5 mmol/l (27.1 mg/100 ml) and 0.09 mmol/l (1.0 mg/100 ml) respectively. In the control group the corresponding values were 4.9 mmol/l (29.5 mg/100 ml) and 0.08 mmol/l (0.9 mg/100 ml). None of the asthmatic children had received intravenous sympathomimetics during their current illness.

The table compares mean plasma antidiuretic hormone and serum sodium concentrations, plasma osmolality, and urine osmolality for the asthmatic

and non-asthmatic groups. The plasma antidiuretic hormone concentrations of asthmatic patients were dramatically increased, the mean being 28.8 pmol/l (12.5 $\mu\text{U}/\text{ml}$) compared with 1.49 pmol/l (0.65 $\mu\text{U}/\text{ml}$) in the non-asthmatic patients ($p < 0.001$, Mann-Whitney test). There were no appreciable differences between the groups in serum sodium concentration, plasma osmolality, or urine osmolality; in all cases the difference between the asthmatic and non-asthmatic groups was non-significant ($p < 0.05$).

Discussion

This study shows a dramatic increase in the levels of plasma antidiuretic hormone in the asthmatic children during a severe asthmatic episode in comparison with non-asthmatic controls. This increase presumably reflects the hyperinflation of the lungs, decreased intrathoracic blood volume, the resultant effects on the baroreceptors, and the subsequent release of antidiuretic hormone from the hypothalamus.¹ While dehydration is frequently claimed to be a complication of severe acute asthma, none of our patients had clinical evidence of dehydration, in terms of serum urea, creatinine, or sodium concentration or serum osmolality. On the other hand, none had evidence of the effects of excessive production of antidiuretic hormone with hyponatraemia and concentrated urine.

There has been only one previous study of plasma antidiuretic hormone levels in status asthmaticus. In this study no control group was used and all but one of the seven patients studied were adults. Higginson and Holliday,⁸ on the basis of hyponatraemia and concentrated urine, suggested that inappropriate secretion of antidiuretic hormone was occurring in five out of 25 children with severe asthma. Recently a report of an adult patient with severe acute asthma and the syndrome of inappropriate antidiuretic

Plasma antidiuretic hormone (ADH) and serum sodium concentrations, plasma osmolality, and urine osmolality for 10 asthmatic and 10 non-asthmatic subjects (values are means, medians in parentheses, and ranges in square brackets)

| | Plasma ADH (pmol/l) | Serum sodium (mmol/l) | Plasma osmolality (mmol/kg) | Urine osmolality (mmol/kg) |
|---------------------------------------|---------------------------------------|--------------------------------------|------------------------------------|-----------------------------------|
| Asthmatic | 28.8 (23.7) [0.91–70.5] 1.49 | 137.9 (138) [135–140] 137.5 | 281 (282) [262–291] 280.8 | 881 (944) [450–1092] 747 |
| Non-asthmatic | (0.82) [0.07–9.16] | (138) [134–141] | (283) [265–288] | (836) [346–1112] |
| Significance (Mann-Whitney U test) | $p < 0.001$ | NS | NS | NS |

NS—not significant.

Conversion: SI to traditional units—ADH: 1 pmol/l = 0.434 $\mu\text{U}/\text{ml}$; sodium: 1 mmol = 1 mEq; osmolality: 1 mmol = 1 mosmol.

hormone secretion was published.⁴ While no actual antidiuretic hormone concentrations were measured, the patient developed other biochemical features suggestive of this syndrome.

The combination of clinical hydration and biochemical "hydration" does not justify the advice that supplementary fluids should be given routinely in acute asthma. The high plasma antidiuretic hormone levels found in our asthmatic patients suggest that supplementary fluids, especially intravenous fluids, may present a danger to the patient.

It is as yet not clear whether the stimulus of oral or intravenous fluids is sufficient to overcome the antidiuretic-hormone-stimulating effects of acute asthma. The hormone has a half life of seven minutes and it may well be "switched off" by treatment aimed at reducing the resistance to flow through the pulmonary vascular bed. Nevertheless, until it is clearly established that this indeed happens, caution should be exercised in administering extra fluids to those with acute asthma, to avoid the potential danger of fluid overload.

References

- ¹ Friedman AL, Segar WE. Antidiuretic hormone excess. *J Pediatr* 1979;**94**:521-6.
- ² Levi J, Coburn J, Kleeman CR. Mechanism of the antidiuretic effect of β -adrenergic stimulation in man. *Arch Intern Med* 1976;**136**:25-9.
- ³ Baker JW, Yerger S, Segar WE. Elevated plasma antidiuretic hormone levels in status asthmaticus. *Mayo Clin Proc* 1976;**51**:31-3.
- ⁴ Benfield GFA, O'Doherty K, Davies BH. Status asthmaticus and the syndrome of inappropriate secretion of antidiuretic hormone. *Thorax* 1982;**37**:147-8.
- ⁵ Geddis DC. *Paediatric handbook*. London: William Heinemann, 1982.
- ⁶ LaRochelle FT, North WG, Stern P. A new extraction of arginine vasopressin from blood: the use of octadecasilyl-silica. *Flugers Arch* 1980;**387**:79-81.
- ⁷ Sadler WA, Lynskey CP, Nicholls MG, Espiner EA. Production of ¹²⁵I-labelled arginine vasopressin for radioimmunoassay. In: Raynaud C, ed. *Proceedings of Third World Congress of Nuclear Medicine and Biology*. Paris: Pergamon Press, 1982:2468-71.
- ⁸ Higer RW, Holliday MA. Acute bronchial asthma and possible inappropriate secretion of antidiuretic hormone. *Pediatr Research* 1973;**7**:428.