Fludrocortisone induced heart failure in Addison’s disease

F. R. WILLIS, G. C. BYRNE and T. W. JONES

Department of Diabetes and Endocrinology, Princess Margaret Hospital for Children, Perth, Western Australia, Australia

Abstract The first reported case of congestive cardiac failure in a child with Addison’s disease secondary to fludrocortisone therapy is presented. A renal adaptation to compensate for chronic salt and water deprivation is suggested as a possible mechanism for the development of congestive cardiac failure in this patient.

Key words: Addison’s Disease; adrenal insufficiency; congestive cardiac failure; fludrocortisone; mineralocorticoid.

CASE REPORT

The authors report the case of a 6 year old boy with autoimmune adrenal insufficiency (Addison’s disease) who developed congestive cardiac failure after 2 weeks on replacement doses of fludrocortisone.

The child presented with a 6 month history of weight loss, lethargy and anorexia. Physical examination demonstrated abnormal pigmentation and postural hypotension. Examination findings were otherwise normal (including assessment of heart size), as was chest X-ray. Initial electrolytes revealed a serum sodium of 126 mmol/L (133-143), serum potassium of 5.8 mmol/L (3.4-5.0), and a urea level of 10.5 mmol/L (2.5-6.0).

Short Synacthen testing confirmed adrenal insufficiency, cortisol level increasing from 66 nm/L to a maximum of 73 nm/L. Serum aldosterone was very low (<70 pmol/L, -ref. 140-970) and plasma renin activity (PRA) elevated (24 ng angiotensin/l s per litre, - ref. 0.3-2.8). Adrenocorticotropic hormone (ACTH) was markedly raised (155 pmol/L, - ref. < 17). Very long chain fatty acid levels were normal. Autoimmune adrenal failure was confirmed by the presence of anti-adrenal antibodies.

Replacement therapy with cortisone acetate (5 mg twice daily) and fludrocortisone (100 µg twice daily) was started. The boy was discharged several days later having improved clinically and with normal plasma electrolytes.

Fourteen days following discharge, he was readmitted with pulmonary and peripheral oedema secondary to fluid overload and cardiac failure. His weight had increased from 19.6 to 24.4 kg. He was tachypnoeic with a respiratory rate of 30 breaths/min. The heart was enlarged clinically and radiologically. A gallop rhythm and systolic ejection murmur were present, and there was 6 cm of palpable hepatomegaly. Blood pressure was normal (105/160 mmHg) and he was afebrile.

Correspondence: F. R. Willis, Chief Registrar, Princess Margaret Hospital for Children, GPO Box D184, Perth, WA 6001, Australia.


Accepted for publication 25 October 1993.

There was no evidence of intercurrent illness nor any suggestion of non-compliance with the treatment regimen. Dispensing error was excluded. Fludrocortisone tablets only come in 0.1 mg form (Florinef, Bristol-Myers Squibb Pharmaceuticals P/L, Noble Park, Vic., Australia). Echocardiography showed a dysfunctional left ventricle that was dilated and had a diminished shortening fraction. Blood electrolytes at this time demonstrated a normal sodium of 139 mmol/L (suggestive of volume expansion) with mild hypokalaemia of 3.3 mmol/L. Serum creatinine was normal at 0.047 mmol/L, as were tests of liver function.

The patient's cortisone acetate was increased to 10 mg, 3 times daily, and his fludrocortisone was ceased. Diuretics (frusemide and spironolactone) were commenced to control the heart failure. Over the next 4 days his cardiac failure resolved and diuretic therapy was withdrawn. On the 7th day echocardiography confirmed normal ventricular size and function. Fludrocortisone was recommenced at a dose of 25 µg twice daily (one quarter the original dose). He was allowed home after 9 days with normal serum electrolytes and no evidence of fluid overload or cardiac dysfunction.

Over the subsequent 3 months it was necessary to increase his fludrocortisone dose to 100 µg daily because of postural hypotension and elevated plasma renin activity.

DISCUSSION

The authors attribute the cardiac failure in this child to fludrocortisone. To the authors' knowledge, the association of congestive cardiac failure with fludrocortisone therapy for Addison’s disease in childhood has not been reported previously. Heart failure was described by Knowlton and Baer in seven adult patients, an average of 30 years after initial diagnosis, all of whom had predisposing cardiovascular disease.1 Geggel et al. reported congestive heart failure in an infant who developed systemic hypertension with fludrocortisone therapy.2 The elevated blood pressure was considered the direct cause for the heart failure.

The patient reported here was commenced on the same dose of fludrocortisone as the infant in Geggel’s report (100 µg twice daily) but differed in that he remained normotensive. The dose in
the child in this report represents approximately 230 μg/m² of surface area per day (less than the comparable dose in an infant on 200 μg daily). Furthermore, there was no suggestion of abnormal myocardial function in the reported patient prior to his episode of congestive cardiac failure, and rapid return to normal function was documented echocardiographically. Dietary sodium intake was assessed as being 30–60 mmol/day from the time of initial diagnosis, which falls within the recommended daily allowance.³

It is reasonable to suppose that in the presence of normal myocardial function, increasing circulating volume would initially produce a corresponding rise in contractility due to the operation of Starling's forces. With increasing volume load, however, the efficiency of myocardial contractility would decline.

Fludrocortisone has similar pharmacokinetics and pharmacodynamics to other glucocorticoids. It is absorbed from the gut, circulates bound to plasma proteins (principally albumin), and is metabolized mainly in the liver. The unbound drug is pharmacologically active.

It has been suggested that development of oedema and cardiac failure with fludrocortisone may be counteracted by the actions of atrial natriuretic factor (ANF) in over-riding the salt retaining effect. ANF is elevated in hyperaldosteronism⁴ and therefore may be raised with mineralocorticoid therapy. ANF also rises with increases in circulating volume.⁵ Thus, in the patient reported here, it could be supposed that ANF would be acting. If so, however, it was ineffective in preventing the development of congestive heart failure.

Although the optimal dose of fludrocortisone for replacement treatment in children with Addison's disease is not known, guidelines as suggested by Forest are usually adequate.⁶ The dose used initially in the reported patient would fall within these guidelines. It is unclear why such a dosage should precipitate congestive cardiac failure in this particular boy.

The authors speculate that a renal adaptation to chronic salt and water deprivation may have played a role in this boy's sensitivity to fludrocortisone. Once mineralocorticoid replacement treatment was begun, this previously adaptive mechanism may have resulted in sodium and water retention leading to congestive heart failure. This hypothesis is supported by the observation that over the following months increased doses of fludrocortisone were needed to maintain sodium homeostasis.

REFERENCES