Fludrocortisone in the treatment of hypotensive disorders in the elderly

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Abstract

Objective—To evaluate tolerance of fludrocortisone in older patients with hypotensive disorders.

Design—Prospective case series.

Setting—Syncope clinic.

Patients—64 Consecutive patients over 65 years (mean age 80 years) with one or more hypotensive disorders (orthostatic hypotension, vasodepressor carotid sinus syncope, and/or vasodepressor neurocardiogenic syncope).

Interventions—Fludrocortisone in daily doses of 100 mg (72%), 50 mg (27%), and 200 mg (one patient).

Main outcome measures—Adverse events, treatment withdrawal.

Results—During follow up 13 patients died of unrelated causes. Of the remainder 33% discontinued fludrocortisone at a mean of five months. Reasons for discontinuing treatment were hypertension, five; cardiac failure, four; depression, three; oedema, three; and unspecified, two. In those who continued treatment supine systolic and diastolic blood pressure did not differ significantly from baseline (follow up two to 21 months). Hypokalaemia developed in 24% at a mean of eight months; in no case was treatment withdrawn because of hypokalaemia.

Conclusion—Fludrocortisone, even in low doses, is poorly tolerated in the long term in older patients with hypotensive disorders.

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Keywords: fludrocortisone; hypotensive disorders; adverse effects; elderly patients

Fludrocortisone is a synthetic mineralocorticoid which increases pressor sensitivity to circulating catecholamines and angiotensin, alters intravascular volume, and has central adrenergic effects.¹ It is beneficial in the treatment of hypotensive disorders: orthostatic hypotension, vasodepressor carotid sinus syndrome, and vasodepressor neurocardiogenic syndrome. In younger patients the most frequently reported adverse events are supine hypertension, cardiac failure, and hypokalaemia.² Fludrocortisone is commonly prescribed for older patients, yet in our clinical experience it is poorly tolerated during prolonged treatment. The objective of this study

was to evaluate tolerance to fludrocortisone in consecutive elderly patients treated for common hypotensive disorders.

Patients and methods

The study population comprised a series of patients over 65 years recruited from the syncope clinic in the Royal Victoria Infirmary during one year. All presented with syncope, dizziness and/or unexplained falls. Baseline investigations included a full clinical assessment, haematology screen, biochemical profile, 12 lead electrocardiogram, 24 hour ambulatory blood pressure monitoring (Space labs, Wokingham, model number 90207), 24 hour ambulatory cardiac monitoring (Delmar, Numed, Sheffield), foot-plate-assisted head up tilt to 70° for 30 minutes, carotid sinus massage (supine and upright), and autonomic function tests.³ All manoeuvres were monitored using continuous blood pressure (Finapres digital photoplethysmography) and heart rate (surface ECG) recording. Supine blood pressures were additionally assessed by sphygmomanometer readings. Patients who had clinical evidence of cardiac failure,⁴ peripheral oedema, or supine systolic blood pressure greater than 180 mm Hg, or biochemical evidence of renal dysfunction (urea and/or creatinine above normal range) were not recruited for fludrocortisone treatment. Participants were reviewed every two weeks, until symptom benefit was achieved and thereafter every two months. At review, patients had supine blood pressure and serum potassium measurement in addition to semi-structured questions about adverse drug events.

DIAGNOSTIC CRITERIA FOR VASODEPRESSOR DISORDERS

Orthostatic hypotension

Orthostatic hypotension was defined as either a fall in systolic blood pressure exceeding 20 mm Hg after two minutes of standing (unsupported) or a fall in systolic blood pressure to less than 90 mm Hg, both in association with symptom reproduction.⁵

Vasodepressor carotid sinus syndrome

Vasodepressor carotid sinus syndrome was defined as a greater than 50 mm Hg fall in systolic blood pressure during carotid sinus massage, either supine or upright, independent of heart rate slowing.⁶

Vasodepressor neurocardiogenic syncope

Type 1, mixed—Heart rate initially increases

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Number of patients who had orthostatic hypotension (OH), vasodepressor neurocardiogenic syncope (VDNCS), and vasodepressor carotid sinus syndrome (VDCSS) before treatment with fludrocortisone.

during head up tilt and later decreases, but remains above 40 beats/min or is less than 40 beats/min only briefly (< 10 seconds).
Type 2, pure vasodepressor—Heart rate increases initially and then decreases to less than 10% of peak value at the time of syncope. A reduction in blood pressure accounts for syncope or presyncope.⁷

Definition of adverse effects
Hypokalaemia is defined as a serum potassium of less than 3.5 mmol/l; hypertension as a supine systolic blood pressure of greater than 200 mm Hg and/or diastolic blood pressure of greater than 100 mm Hg; cardiac failure was classified by New York Heart Association criteria.⁴

Results
Sixty four elderly patients were studied: mean age 80 (range 58–98 years); 22 were male. Fludrocortisone was prescribed for orthostatic hypotension in 17; vasodepressor carotid sinus syndrome in 19; combined vasodepressor carotid sinus syndrome and orthostatic hypotension in 14; combined vasodepressor carotid sinus syndrome and vasodepressor neurocardiogenic syndrome in four; combined vasodepressor neurocardiogenic syndrome and orthostatic hypotension in seven; and combined vasodepressor neurocardiogenic syndrome, orthostatic hypotension, and vasodepressor carotid sinus syndrome in three (figure). The mean duration of treatment was one year (range 2 to 21 months). The initial

daily doses of fludrocortisone were 50 µg in 17 (27%) patients, 100 µg in 46 (72%) patients, and 200 µg in one patient. The dose of fludrocortisone was increased by increments of 50 mg either until symptoms were abolished (for orthostatic hypotension, vasodepressor carotid sinus syndrome, and vasodepressor neurocardiogenic syndrome) or the orthostatic fall in systolic blood pressure was less than 10 mm Hg (for orthostatic hypotension) or until adverse events occurred. Final doses of fludrocortisone were 50 µg in 16 (25%), 100 µg in 38 (59%), and 200 µg in eight (12%) .
Adverse events occurred in 38 patients: hypertension in four, cardiac failure in seven, hypertension and stroke in one, depression in three, and hypokalaemia in eight. Thirteen patients died during the follow up period (table 1) and two reported no treatment benefit and discontinued medication. Fludrocortisone was withdrawn in 17 patients after a mean of five months (range 1 day–12 months). Hypokalaemia developed at a mean of eight months (range 2–21); in no case was treatment withdrawn because of hypokalaemia (table 2).
Discussion
The prevalence of hypotensive disorders increases with advancing years. The commonest diagnoses are orthostatic hypotension, vasodepressor carotid sinus syndrome, and neurocardiogenic syndrome. These hypotensive diagnoses are responsible for symptoms in 43% of older patients referred to a specialist syncope service.⁸ A combination of one or more diagnoses occurs in 20%.⁸ Treatment options for vasodepressor disorders are limited. Treatment includes practical manoeuvres (for example, stand slowly, avoid prolonged standing or Valsalva-like movements); physiological adjustments (for example, increased salt and fluid intake, elastic support garments, and elevation of the bed head); and pharmacological approaches. Drugs used are fludrocortisone,^{9,10} prostaglandin inhibitors,¹¹ somatostatin analogues,¹² dopaminergic antagonists,¹³ midodrine,^{14,15} ergotamine,¹⁶ xamoterol,¹⁷ and fluoxetine.¹⁸
Fludrocortisone is generally regarded as the most effective first line treatment^{10,12,19} in orthostatic hypotension. For the other treatments cited, the evidence for benefit is small or the occurrence of adverse effects is frequent or large intervention studies have not been reported. Studies of therapeutic options for the treatment of vasodepressor carotid sinus syndrome are even more limited. Preliminary data suggested benefit in symptom control and degree of carotid sinus vasodepression with fludrocortisone in the very old patients (mean 80 (5) years) who were treated for a six month period. However, supine systolic hypertension (mean 171 (37) mm Hg) developed in over half of these patients after only two weeks of treatment.¹¹ Treatment for recurrent neurocardiogenic syndrome which is predominantly vasodepressor also focuses on fludrocortisone, in addition to β-adrenergic blocking drugs,²⁰

Table 1 Primary causes of death in 13 patients who died during treatment with fludrocortisone

Causes of death	Number of patients	Treatment duration (mnh)
Infection	4	9
Neoplasm	6	5
Myelodysplasia	1	18
Myocardial infarct	1	0.5
Aortic aneurysm	1	5

Table 2 Adverse events in 38 of 64 patients treated with fludrocortisone

Adverse event	No of patients	Mean duration (mnh) of treatment	Mean dose (µg)	No of patients withdrawn
Cardiac failure	7	7	93	7
Systolic hypertension	4	5	75	4
Stroke	1	2	100	1
Depression	3	4	100	3
Hypokalaemia	8	8	100	0
No benefit	2	3	75	2
Deaths	13	7	92	0

disopyramide,²¹ α -1 agonists¹⁵ and serotonin re-uptake inhibitors.²² However, no data from large randomised control studies are available.

9 α -Fludrocortisone is a synthetic mineralocorticoid, which increases pressor sensitivity to circulating catecholamines and angiotensin, alters intravascular volume, and has central adrenergic effects.¹ Its benefit in vasodepressor disorders is probably due to one or more of these physiological influences. Adverse effects have previously been reported in a small proportion of younger patients with idiopathic and diabetic orthostatic hypotension.^{2,9} In these patients, systolic hypertension and cardiac failure were attributed to sodium retention and plasma volume expansion.² During long term treatment, it was noted that although plasma volumes returned to control levels, systolic blood pressure continued to rise because of enhanced peripheral vascular resistance. This was attributed to increased sensitivity to circulating catecholamines.² In the present study, these adverse effects are even more frequent, although plasma volumes were not measured in this series. It is possible that patients who have an idiopathic relative reduction in plasma volume do better on fludrocortisone and have fewer side effects.

Increased susceptibility to adverse drug effects with advancing years is well documented. This is because of a combination of co-morbidity, polypharmacy, altered volume regulation, impaired baroreflex sensitivity, and age related changes in vascular resistance.²³ In keeping with this, over a third of subjects experienced adverse effects during treatment with fludrocortisone and a quarter required withdrawal of drug therapy despite use of relatively low doses.

Fludrocortisone can be useful in the short term for symptomatic control of hypotensive disorders in the elderly. Fludrocortisone during prolonged treatment is poorly tolerated, even in low doses.

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LETTERS TO THE EDITOR

Scope

Heart welcomes letters commenting on papers published in the journal in the previous six months. Topics not related to papers published earlier in the journal may be introduced as a letter: letters reporting original data may be sent for peer review.

Presentation

Letters should be:

- not more than 600 words and six references in length
- typed in double spacing (fax copies and paper copy only)
- signed by all authors.

They may contain short tables or a small figure. **Please send a copy of your letter on disk.** Full instructions to authors appear in the January 1997 issue of *Heart* (page 89).

Prospective relations between *Helicobacter pylori* infection, coronary heart disease and stroke in middle-aged men

SIR,—In our nested case-control study of *Helicobacter pylori* infection and coronary heart disease,¹ based on the British Regional Heart Study cohort, men with pre-existing coronary heart disease were unintentionally under-represented among the controls selected (4% v 21% expected). This problem has been documented in the *Lancet*² in relation to a parallel study of the relation between homocysteine and stroke.³ However, the results of the study of *H pylori* and its associations with coronary heart disease and stroke are not materially affected by this under-representation. This is emphasised by the results presented in the paper showing that the odds ratio associated with *H pylori* infection for coronary heart disease was very similar if men with pre-existing disease were completely excluded. Our conclusion therefore remains unchanged.

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Probable right ventricular dysplasia and patent foramen ovale presenting with cyanosis and clubbing in a patient with characteristics of Noonan syndrome

SIR,—I report additional information on a case described by myself and Da Costa.¹ The patient, who presented with cyanosis and clubbing, was described as having *probable* right ventricular dysplasia associated with

patent foramen ovale. She also had characteristics of Noonan syndrome. Right ventricular endomyocardial biopsy specimens showed fibre hypertrophy, vacuolation, and degeneration with fine interstitial fibrosis; however, fatty infiltration was not seen. Despite the presence of one major criterion for diagnosis of right ventricular dysplasia (severe dilatation and reduced ejection fraction of the right ventricle without left ventricular impairment), and one minor criterion (T wave inversion in leads V1–V4 on ECG), there were insufficient criteria for definitive diagnosis of right ventricular dysplasia.²

The original report pointed out that the patchy nature of fatty infiltration in the right ventricle can result in failure of endomyocardial biopsies to sample an area of fatty infiltration. Thus, the criteria used for diagnosis often prevents diagnosis during the patient's life; they are later confirmed at post mortem examination to have right ventricular dysplasia.

Our patient has since undergone right ventricular cardiomyopathy with closure of the foramen ovale (by Professor Sir Magdi Yacoub) with clinical benefit. Transmural biopsies taken at that time from the left ventricle were normal. Right ventricular biopsies showed no myocardial tissue but extensive fibrous and fatty tissue (personal communication, Dr M Burke, consultant histopathologist, Mount Vernon Hospital, Middlesbrough). This additional information confirms that the patient satisfied the criteria for a diagnosis of right ventricular dysplasia.

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- 1 Wilmshurst P, Da Costa P. Probable right ventricular dysplasia and patent foramen ovale presenting with cyanosis and clubbing in a patient with characteristics of Noonan syndrome. *Br Heart J* 1995;74:471–5.
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Echocardiographic evaluation of ventricular diastolic function: implications for treatment

SIR,—In their recent editorial Brecker and Gibson suggest an alternative approach to assessing the effects of treatment in diastolic dysfunction, namely to identify changes in diastolic measurements occurring with treatment that are known to increase exercise tolerance or improve prognosis.¹

Although exercise limitation is the obvious outcome for patients with clinically significant diastolic dysfunction and indeed any functional limitation is likely to be more evident on exercise, nearly all studies report on resting parameters of diastolic performance. Despite increasingly widespread use of stress echocardiographic data in the definition of myocardial ischaemia, systolic dysfunction, and exercise related valve dysfunction, the role of exercise based echocardiographic indices of cardiac relaxation have to date been largely ignored. The reason for this is unclear.

Studies conducted during exercise may

increase our ability to define abnormal relaxation and both link this directly to impairment of exercise capacity and assess the effects of candidate treatments. We have previously assessed the effects of brain natriuretic peptide (BNP) infusion on exercise haemodynamics in isolated diastolic dysfunction.² We found that BNP significantly attenuated the exercise induced rise in pulmonary capillary wedge pressure in patients with diastolic dysfunction. In this study, we used invasive haemodynamic monitoring but it is our belief that exercise diastolic performance can be assessed non-invasively with Doppler echocardiography. To achieve this, non-invasive echocardiographic surrogate measures of ventricular filling pressure on exertion need to be explored and validated.

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CORRECTIONS

Fludrocortisone in the treatment of hypotensive disorders in the elderly

RM Hussain, SJ McIntosh, J Lawson, RA Kenny (*Heart* 1996;76:507–9).

Under "Interventions" in the abstract it should have read: Fludrocortisone in daily doses of 100 µg (72%), 50 µg (27%), and 200 µg (one patient). And not as published.

Effects of increasing flow rate on aortic stenotic indices: evidence from percutaneous transvenous balloon dilatation of the mitral valve in patients with combined aortic and mitral stenosis

T-M Lee, S-F Su, M-F Chen, C-S Liao, Y-T Lee (*Heart* 1996;76:490–4).

Dr Sheng-Fang Su's name was misspelled in the article.

NOTICES

The 1997 Annual Conference of the British Cardiac Society will take place at G-MEX, Manchester from 20–22 May. For further information, please contact the British Cardiac Society, 9 Fitzroy Square, London W1P 5AH. (Tel: +(0) 171 383 3887; fax: +(0) 171 388 0903; e-mail: bcs@rbh.nthames.nhs.uk) or visit <http://www.bcs.rbh.nthames.nhs.uk> on the Internet.

Asian-Pacific Cardiovascular Update will be held from June 5–6 in Hong Kong. For further information, contact Professor JE Sanderson, Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong. (e-mail: jesanderson@cuhk.edu.hk).