PAPERS AND SHORT REPORTS

Effect of stilboestrol on sodium balance, cardiac state, and renin-angiotensin-aldosterone activity in prostatic carcinoma

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Abstract

A prospective study examined the sequential effects of diethylstilboestrol (stilboestrol) on sodium balance, cardiac state, and renin-angiotensin-aldosterone activity in six patients with metastatic carcinoma of the prostate. Whereas metabolic balance studies did not show evidence of sodium retention during the first seven days of treatment, there was a significant and progressive increase in plasma volume after three months (mean increase 541 ml; $p < 0.01$). Stilboestrol increased supine plasma renin and angiotensin II values but the response of renin-angiotensin-aldosterone activity to erect posture was progressively reduced during treatment. No significant changes in blood pressure or indices of cardiac function occurred during the three months of observation.

The findings of increased basal renin-angiotensin-aldosterone activity and an increase in plasma volume suggest an important mechanism of the cardiac complications associated with oestrogen treatment.

Introduction

Since the work of Huggins and Hodges hormonal manipulation has been the mainstay treatment of metastatic carcinoma of the prostate.¹ Orally administered oestrogens, usually diethylstilboestrol (stilboestrol), however, have been associated with an

increased risk of cardiovascular complications from pulmonary emboli, cerebrovascular accidents, myocardial infarction, and congestive cardiac failure.^{2,3} Although widely recognised as a clinical problem, the mechanisms underlying the cardiac complications—particularly congestive heart failure and hypertension—have not been fully elucidated. The present study was designed to assess in detail the sequential effects of stilboestrol on electrolyte balance, renin-angiotensin-aldosterone activity, and cardiac state in a small group of patients with prostatic carcinoma and normal cardiovascular function.

Subjects and methods

Patients beginning hormonal treatment with oral stilboestrol for metastatic carcinoma of the prostate were considered for the study. Criteria for exclusion included a history of congestive heart failure, deep venous thrombosis, pulmonary emboli, hypertension, diabetes, plasma creatinine concentration over 180 $\mu\text{mol/l}$ (2.0 mg/100 ml), or recent major surgery; treatment with any of the following: anti-inflammatory and antiprostaglandin agents, antihypertensives, β blockers, diuretics, and cytotoxics; and a need for immediate antiandrogen treatment—for example, for disabling bone pain. The protocol was approved by the ethical committee of the Canterbury Hospital Board, and all patients gave informed consent.

STUDY DESIGN

After diagnosis of metastatic carcinoma of the prostate the patients were admitted for metabolic studies before and immediately after beginning stilboestrol. They were given a normal diet according to individual preferences but which for 10 days remained fixed in respect of sodium (range 70–130 mmol(mEq)/24 h in individual patients) and potassium (40–66 mmol (mEq)/24 h) content. Fluid intake was fixed at 1500 ml/24 h during the same period. Stilboestrol 1.0 mg three times a day was begun on day 3 of admission. Blood samples for estimation of plasma renin activity⁴ and angiotensin II⁵ and aldosterone⁶ concentrations were drawn supine (8 am) and after one hour of erect posture (9 am) on the day before starting stilboestrol and again two and seven days after starting treatment. Samples for repeat hormone studies were taken four and 12 weeks later. Plasma cortisol (kits from Diagnostic Products, Los Angeles) and arginine vasopressin⁷ concentrations were measured at specified intervals. Urinary

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excretion of sodium, potassium, creatinine, and aldosterone was measured in 24 hour urine collections by standard techniques. Left ventricular ejection fraction and left ventricular end diastolic volume were measured using M mode echosonography by the same operator before and at standardised intervals after beginning treatment. Plasma volume was measured by Evans blue (colorimetric assay) before and at seven, 30, and 90 days after beginning treatment. Blood pressure was measured at 8 am (supine) on each occasion by the same physician (NG or JC) using routine cuff sphygmomanometry.

After completing the metabolic balance study patients were reviewed as outpatients two and eight weeks after beginning stilboestrol for clinical assessment and measurement of plasma testosterone and urinary stilboestrol. At four and 12 weeks the patients were readmitted overnight for repeat hormonal and cardiovascular measurements.

Results are expressed individually in tables and as the mean and standard error of the mean (SEM) in figures and text. Levels of statistical significance were obtained by paired Student's *t* tests.

Results

Six patients satisfied the criteria for entry. All had stage IV carcinoma of the prostate confirmed by raised serum acid phosphatase activity or an abnormal bone scan, or both, with pelvic and para-aortic lymphadenopathy detected by CT scan in case 3. Table I lists their ages and other details. During the study one patient (case 1) died of progressive metastatic carcinoma. He had an initial response to hormonal treatment with relief of

Electrolytes, plasma volume, and cardiac state—There was no consistent effect of stilboestrol on sodium excretion during the 10 days of controlled sodium intake (table II). Body weight did not change significantly and there were no changes in plasma sodium or potassium concentrations. Table I and figure 1 show the sequential changes in plasma volume over three months of stilboestrol treatment. A mean increase of 541 ml at 90 days was highly significant ($p < 0.01$) when compared with pretreatment values. There was no consistent change in haemodynamic indices in any patient: blood pressure did not increase and there were no significant changes in left ventricular ejection fraction or left ventricular end diastolic volume (table I).

Hormone changes—Basal supine (8 am) plasma renin activities and angiotensin II concentrations increased within six days after beginning stilboestrol and there was a significant increase in urine aldosterone excretion, though plasma aldosterone did not change (tables II, III). At four and 12 weeks of treatment basal plasma renin activity and angiotensin II concentrations had increased further and were significantly higher than pretreatment values (as was aldosterone at four weeks). Plasma cortisol also increased significantly from the sixth day of treatment (mean 437 nmol/l (15.8 µg/100 ml) before treatment, 810 nmol/l (29.3 µg/100 ml) on day 6, 1213 nmol/l (43.9 µg/100 ml) on day 30, 1243 nmol/l (45.0 µg/100 ml) on day 90; $p < 0.01$, $p < 0.05$, $p < 0.05$, respectively). There were no significant changes in plasma arginine vasopressin concentrations during stilboestrol treatment (mean 9.6 pmol/l (10.4 pg/ml) before treatment, 6.3 pmol/l (6.8 pg/ml) on day 6, 7.1 pmol/l (7.7 pg/ml) on day 30, 5.1 pmol/l (5.5 pg/ml) on day 90). Despite the increases in basal supine hormone concentrations the response of renin-angiotensin-aldosterone activity to erect posture was greatly

TABLE I—Clinical and haemodynamic data in six patients before and during treatment with stilboestrol

Case No	Age (years)	Weight change after 90 days' treatment (kg)	Supine blood pressure (mm Hg)			End diastolic volume (ml)		Left ventricular ejection fraction (%)		Plasma volume change after 90 days' treatment (ml)
			Before treatment	1 month	3 months	Before treatment	3 months	Before treatment	3 months	
1	61	*	128/74	180/65	*	128	*	46	*	(+196 at 1 month)
2	71	-0.6	132/74	166/68	166/55	145	142	60	59	+416
3	58	+0.5	155/88	140/85	130/74	148	152	58	67	+941
4	66	+0.4	126/68	126/60	138/78	108	127	24	45	+429
5	58	+1.8	150/90	140/80	144/87	135	151	66	66	+180
6	75	+0.3	145/75	130/60	146/88	167	154	70	69	+693

* Patient died at two months.

FIG 1—Change in plasma volume after start of stilboestrol (arrow). Points are means. Bars are SEM.

* Compared with pretreatment volume: $p < 0.01$.

pain but at one month it was obvious that his disease had advanced. Results at three months were therefore from five patients only. Another patient (case 2) developed angina with effort and was treated with oral glyceryl trinitrate. The remaining patients did not encounter any problems during the study. Compliance in all patients was confirmed by tests for stilboestrol in urine as well as detecting a reduction in plasma testosterone (mean 19.7 (SEM 5.3) nmol/l (5.7 (1.5) ng/ml) before stilboestrol, 1.2 (0.2) nmol/l (0.3 (0.06) ng/ml) at two weeks; $p < 0.05$) and increasing sex hormone binding globulin concentrations (mean 58 (SEM 15) units before stilboestrol, 339 (55) units at two weeks; $p < 0.001$).

FIG 2—Effect of stilboestrol (arrow) on hormone responses to upright posture. Y axis represents postural increment in hormone value as percentage of supine value. Points are means. Bars are SEM.

* Compared with pretreatment value: $p < 0.01$.

TABLE II—Urinary excretion of sodium and aldosterone in patients receiving constant intake of sodium. Values are means of three consecutive daily measurements

Case No	Days before stilboestrol	Days 1-3 of stilboestrol	Days 4-6 of stilboestrol
<i>Sodium excretion (mmol/24 h)</i>			
1	98.6	88.6	97.0
2	71.0	90.3	88.0
3	105.3	58.3	92.0
4	88.3	85.3	72.3
5	136.3	135.3	143.3
6	37.0	37.6	50.6
Mean (SEM)	89.4 (12.5)	82.6 (12.4)	90.5 (11.5)
<i>Aldosterone excretion (nmol/24 h)</i>			
1	24.0	31.0	37.0
2	16.0	18.3	30.3
3	29.3	30.3	38.0
4	17.3	14.6	25.6
5	3.3	7.6	10.0
6	10.3	15.3	12.3
Mean (SEM)	16.7 (3.5)	19.5 (3.5)	25.5 (4.5)*

* Compared with value before stilboestrol: $p < 0.05$.

Conversion: SI to traditional units—Sodium: 1 mmol/24 h = 1 mEq/24 h. Aldosterone: 1 nmol/24 h = 0.36 µg/24 h.

TABLE III—Resting (8 am) and upright (9 am) hormone values in six patients before and during treatment with stilboestrol

Case No	Day before		Day 2		Day 6		Day 30		Day 90	
	8 am	9 am	8 am	9 am	8 am	9 am	8 am	9 am	8 am	9 am
<i>Plasma renin activity (nmol/l/hr)</i>										
1	0.57	3.45	1.18	5.19	0.99	3.29	1.19	2.23	†	†
2	0.26	1.14	0.34	0.82	0.45	0.79	1.28	1.83	0.81	0.85
3	0.79	3.45	1.02	3.91	0.85	2.81	1.52	2.08	1.55	1.46
4	0.22	1.65	0.36	4.53	1.00	2.75	1.34	3.01	1.87	2.78
5	0.15	0.32	0.18	0.53	0.46	1.16	0.51	0.54	0.69	0.92
6	1.31	2.88	0.52	7.16	0.76	3.78	2.38	2.92	0.65	0.64
Mean	0.55	2.15	0.60	3.69	0.75*	2.43	1.37***	2.10	1.11	1.33
SEM	0.18	0.49	0.17	0.96	0.10	0.44	0.25	0.33	0.25	0.35
<i>Plasma angiotensin II (pmol/l)</i>										
1	13	45	21	56	17	44	13	21	†	†
2	14	32	18	25	27	30	30	27	34	27
3	22	51	36	58	48	49	37	38	39	37
4	12	33	12	76	21	54	21	82	31	107
5	30	44	30	47	38	65	48	62	48	49
6	9	23	11	37	23	25	35	34	28	22
Mean	17	38	21	50	29**	45	31***	44	36***	48
SEM	3	4	4	7	5	6	5	9	4	14
<i>Plasma aldosterone (pmol/l)</i>										
1	242	631	463	646	176	480	391	541	†	†
2	263	549	256	442	233	467	600	465	366	594
3	317	619	218	490	184	515	365	379	357	383
4	131	254	116	316	158	305	197	236	184	185
5	116	472	100	408	145	480	122	370	146	388
6	145	252	110	565	82	291	191	377	84	72
Mean	202	463	211	478	163	423	261*	395	227	324
SEM	34	64	56	44	20	27	44	38	57	81

† Patient died at two months.

Compared with value before stilboestrol: * $p < 0.05$; ** $p < 0.02$; *** $p < 0.01$.

Conversion: SI to traditional units—Renin activity: 1 nmol/l/h = 1.3 ng/ml/h. Angiotensin II: 1 pmol/l = 0.99 pg/ml. Aldosterone: 1 pmol/l = 0.36 µg/ml.

reduced by stilboestrol (fig 2). The increment (expressed as a percentage of supine value) in plasma renin activity and angiotensin II and aldosterone values fell progressively during stilboestrol treatment.

Discussion

Fluid retention and haemodynamic disorders are common complications of oestrogen treatment in patients with prostatic cancer, yet the underlying cause of these complications is largely unknown. Detailed study of salt and hormone balance is difficult in ill patients, in whom drug interference and diminished compliance may complicate any long term evaluation. Changes in activity of the renin-angiotensin-aldosterone system have been postulated as causal factors⁹ but no sequential study of hormonal and cardiac state has been undertaken. This study therefore examined in detail a

small group of patients without cardiovascular disease and in whom drug interference was minimised.

Our results show clearly that during stilboestrol treatment there is expansion of the plasma volume. There was clear evidence of early and sustained activation of the renin-angiotensin-aldosterone system and a definite abnormality in response of this system to erect posture. Unlike a study of postmenopausal women¹⁰ and the findings of Johnson and Davis in dogs¹¹ our study did not show a direct sodium retaining action of stilboestrol, at least in the short term. If plasma volume increases without change in reabsorption of sodium, oestrogens may be acting to redistribute body fluids so that extracellular fluid volume expands at the expense of intracellular volume. Despite this expansion in plasma volume basal plasma renin activities and angiotensin II concentrations increased rapidly and were sustained above prestudy values for at least three months. While there is good evidence in women that oestrogens increase renin (both renin substrate¹²⁻¹⁶ and renin concentration¹⁶), there is less evidence of activation of the renin-angiotensin-aldosterone system in men.¹² A previous study in patients with prostatic cancer¹⁷ showed no change in plasma renin activity during oestrogen

treatment. From our findings, however, it is evident that plasma renin activity and angiotensin II and aldosterone values increase with long term stilboestrol but that the expected response to the erect posture (fig 2) becomes progressively reduced. Whether this diminution in responsiveness to erect posture is due to the associated plasma volume expansion, direct inhibition of renin secretion by higher angiotensin II concentrations, or other mechanisms cannot be determined from our study. Interestingly, most other states of hyperreninaemia are associated with an increased response of renin-angiotensin-aldosterone activity to erect posture.^{18,19} The different behaviour of patients treated with oestrogen may follow from the action of oestrogen to increase renin substrate concentrations,¹²⁻¹⁶ whereas in other hyperreninaemic states presumably there is a direct stimulus to renin secretion.

Although our patients showed no sign of cardiac dysfunction or hypertension during stilboestrol treatment, the combination of

plasma volume expansion and an increase in plasma angiotensin II and aldosterone concentrations might be hazardous in patients with heart disorders or a tendency to hypertension. The findings of this study suggest an important mechanism of the cardiac complications associated with oestrogen treatment and reaffirm the need carefully to evaluate cardiac and haemodynamic state in patients with prostatic cancer before deciding on the form of treatment.

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Value of routine follow up of women treated for early carcinoma of the breast

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Abstract

The value of routine follow up of women treated for early breast cancer by mastectomy with or without postoperative radiotherapy was assessed retrospectively. Over eight years 546 patients made 6863 clinic visits, during which 192 first relapses were detected. Ninety three relapses were detected at scheduled (routine) visits and 99 at unscheduled (interval) visits. First relapses within the treated area or in the contralateral breast were detected significantly more commonly at routine visits than were first metastatic relapses (66/89 (74%) compared with 27/103 (26%)). Patients whose local relapse was detected at a routine visit had a significantly better survival than those whose local relapse was detected at an interval visit. A relapse that was potentially curable (local or in the contralateral breast) was detected at 66 (1%) of 6764 routine visits, but only 26 (39%) of these patients remained free of disease.

It is concluded that the intensity of follow up of such patients could be reduced without any adverse effect on prognosis but with appreciable financial and other benefits.

Introduction

Routine follow up of patients after definitive treatment for malignant disease forms a major part of the workload of most radiotherapy and many surgical clinics. Follow up may be for a variety of reasons, including assessing the efficacy of treatment and its morbidity, helping patients to come to terms with their illness, teaching, and, especially for less common conditions, gaining an understanding of the clinical course of the disease. The main purpose of follow up, however, is to detect relapse at a stage at which effective secondary management can be begun, and it is this that generally determines the frequency of attendance. Though some patients undoubtedly find follow up reassuring, many others find it a considerable source of stress. Regular attendance is costly not only for the patient, who may have to pay for transport or take time off work, but also in terms of the use of National Health Service resources.

The value of routine follow up has been questioned,^{1,3} but few studies have examined the effectiveness of follow up in detecting relapse and what influence, if any, this has on a patient's subsequent clinical course.^{4,5} Breast cancer is the most common malignancy in women, and this study examined the value of routine follow up of women after primary treatment for early breast cancer by mastectomy alone or by mastectomy and postoperative radiotherapy.

Patients and methods

During 1974-7 inclusive 717 women were referred to this department with a diagnosis of carcinoma of the breast, which was clinically staged as

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