Mean (and range) results for patients who completed two weeks of treatment with all three drugs

	Paracetamol	Sulindac	Indomethacin	n	p Value*
Mean arterial pressure (mm Hg):					
Lying	103·8 (81·0-120·0)	109·9 (87·0-138·3)	117·8 (102·6-152·0)	18	<0·001
Standing	102·4 (78·0-123·6)	106·8 (91·0-138·6)	116·4 (99·3-133·3)	18	<0·001
Body weight (kg)	81·4 (56·2-108·8)	81·5 (56·4-109·5)	81·7 (56·8-108·5)	17	NS
Pain score (mm)	63 (23-98)	49 (20-95)	46 (8-82)	15	<0·05
Stiffness score (mm)	67 (6-98)	52 (14-97)	48 (7-98)	15	<0·05
Reasons for stopping treatment:					
Poor symptom relief	19	3	3	21	<0·001
Side effects		3	8	21	<0·01
Total	19	6	11	21	<0·001

*Significance of difference among all three treatments by analysis of variance or χ^2 test with Yates's correction.

visual analogue scales), and counts of unused tablets were recorded at intervals of two weeks throughout the study. Blood pressure (phase V diastolic, right arm) was measured with a random zero sphygmomanometer by an observer who was unaware of the treatment taken. Mean arterial pressure was calculated as diastolic pressure plus one third of pulse pressure.

Many phases of treatment had to be shortened to two weeks (see table), and we therefore analysed the results after two weeks. The three drugs were compared using Friedman's two way analysis of variance followed by Wilcoxon's test for matched pairs. All data, including those for four and six weeks of treatment, were also examined by analysis of variance using multiple linear regression.

The table shows the results after two weeks. The mean arterial pressure was significantly higher with indomethacin than paracetamol ($p<0·001$ lying and standing), higher with sulindac than paracetamol (NS), and significantly higher with indomethacin than sulindac ($p<0·01$ lying and $p<0·001$ standing). Nine patients completed six weeks' treatment with both sulindac and indomethacin. Their mean arterial pressure remained significantly higher with indomethacin than sulindac, with differences after six weeks of 12·5 (SE 5·3) mm Hg lying ($p<0·05$) and 14·6 (5·2) mm Hg standing ($p<0·02$).

Analysis of the total (six week) data by multiple linear regression showed a significant ($p<0·05$) increase in body weight during treatment with indomethacin compared with paracetamol (0·48 kg) and sulindac (0·35 kg). There was a highly significant positive correlation between changes in body weight and changes in mean arterial pressure ($p<0·005$). Scores for pain and stiffness during treatment with indomethacin and sulindac were similar and significantly lower than those for paracetamol.

Comment

These results show that indomethacin has a substantial and sustained pressor effect in treated hypertensive patients. The small but significant increase in body weight during treatment with indomethacin, and the positive correlation between changes in body weight and blood pressure, suggest that the pressor effect may be partly due to retention of salt and water. Sulindac did not increase blood pressure significantly compared with paracetamol. This does not exclude a pressor action of sulindac, as the 95% confidence limits indicate that it may increase lying mean arterial pressure by as much as 11·9 mm Hg, though its effect is significantly less than that of indomethacin. The data on symptoms and side effects must be viewed with caution because this was an open study, but they suggest that sulindac was as effective and well tolerated as indomethacin.

We suggest that sulindac should be preferred to indomethacin in hypertensive patients requiring a non-steroidal anti-inflammatory drug.

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Antithrombin III concentration, thrombosis, and treatment with luteinising hormone releasing hormone agonist in prostatic carcinoma

Treatment of advanced carcinoma of the prostate is based mainly on the assumption that the tumour is androgen dependent. In the past oestrogens have been used most commonly as endocrine treatment. Serious exacerbation of thromboembolic complications during oestrogen treatment, however, prompted investigation of alternative means of androgen suppression.[1] In 1980 Tolis *et al* showed that testosterone could be suppressed by giving agonists of luteinising hormone releasing hormone, which might thus be used instead of oestrogens.[2] The mechanism of the thrombogenic effect of oestrogens is unclear, but recent studies suggested that of all the effects of blood clotting induced by oestrogen treatment of prostatic cancer, the fall in plasma antithrombin III concentration is the most important.[3,4]

Before agonists of luteinising hormone releasing hormone are introduced as endocrine treatment for prostatic cancer it is essential to establish whether they influence clotting in the same way as oestrogens. We therefore measured antithrombin III concentrations in patients with carcinoma of the prostate before and during treatment with the luteinising hormone releasing hormone agonist ICI 118.630 depot to estimate the risk of thromboembolic events.

Patients, methods, and results

Thirty men aged 55-84 (mean 72) with cytologically confirmed carcinoma of the prostate were included in the study. All had locally advanced disease or distant metastases, or both. None had previously received endocrine treatment. An agonist of luteinising hormone releasing hormone (ICI 118.630 depot; 3·6 mg) was injected into the skin of the anterior abdominal wall at intervals of 28 days. The plasma concentration of antithrombin III was measured by a technique that uses the chromogenic substrate S-2238 (Kabi Diagnostica, Mölndal, Sweden); the normal range for adults is 80-120%. Samples were taken one day before and one, two, and three months after the start of treatment. The endocrine effect of the treatment was assessed by repeated determination of plasma testosterone, luteinising hormone, and follicle stimulating hormone concentrations. The significance of mean differences in values during treatment compared with the baseline values was determined by Fisher's test.

The mean baseline concentrations of antithrombin III were within the normal range at 103·23 (SD 14·18)%. No significant change took place during treatment, the concentrations one, two, and three months after the start of treatment being 100·97 (14·58)%, 103·07 (13·45)%, and 103·20 (13·92)% respectively. The mean plasma concentrations of luteinising hormone and follicle stimulating hormone fell significantly ($p<0·001$), and the mean plasma testosterone concentrations were significantly suppressed ($p<0·001$) to values seen after castration.

Comment

Epidemiological studies and clinical experience have shown that treatment of prostatic cancer with high doses of oestrogen increases the morbidity and mortality from cardiovascular disease. Studies seeking to establish the mechanism of this phenomenon have focused on coagulation and the fibrinolytic system. Recent studies have shown that antithrombin III concentrations are reduced during oestrogen treatment in patients with carcinoma of the prostate, and this might contribute to these patients' increased incidence of cardiovascular complications. One quick way of obtaining information about the risk of undesirable effects of a new form of endocrine treatment is to study laboratory variables indicating or contribut-

ing to a changed risk of complications. With such an approach a prospective short term study in a limited number of patients will yield valuable information for longer trials.

In the present study no significant changes in antithrombin III concentrations occurred during treatment with a depot preparation of an agonist of luteinising hormone releasing hormone. This indicates that the treatment does not aggravate the risk of thromboembolism in the same way as oestrogens do. Limited clinical observations also suggested that treatment with the agonist is associated with fewer undesirable cardiovascular side effects than treatment with oestrogens.[5] There are probably no indications for stopping treatment with the agonist before major surgery, as is recommended with oestrogen treatment.

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Change in skin thickness associated with cheiroarthropathy in insulin dependent diabetes mellitus

Rosenbloom and Frias described three insulin dependent diabetics who had thick, waxy skin and limited mobility of large and small joints.[1] Further studies have shown that the prevalence of limited joint mobility affecting mainly the small joints of the hand (cheiroarthropathy) in insulin dependent diabetics varies from 8% to 36%.[2] The precise cause of this limited joint mobility is not known, but it has been suggested that a structural alteration in collagen may be a factor.[2] We measured the thickness of the skin in young insulin dependent diabetics using a pulsed ultrasound technique and related the results to the presence of cheiroarthropathy.

Subjects, methods, and results

Ninety two insulin dependent diabetics aged 20-38 were selected from outpatients regularly attending the diabetic department at this infirmary. The diabetes was of short duration (less than 18 months) in 26 (16 men, 10 women) and of longer duration (more than 10 years) in 66 (48 men, 18 women). A group of non-diabetic controls comprised 40 healthy volunteers (20 men, 20 women) aged 20-38. The thickness of the skin (epidermal surface to interface of dermis and fat) was measured with a Cutech dermal depth detector (Steifel Laboratories, Slough, Berks) using an ultrasound A scan system.[3] The sites on the skin selected for measurement were the flexor surfaces of both mid-forearms 10 cm proximal to the distal wrist crease and the medial aspect of both upper arms 10 cm proximal to the antecubital fossa. The mean of these four measurements was taken as the thickness of the skin of the subject. Limited joint mobility as a measure of cheiroarthropathy was evaluated independently by two observers using the "prayer" manoeuvre outlined by Rosenbloom *et al*.[4]

The results in the normal subjects and in the groups of patients with diabetes of long and short duration were analysed using Student's *t* test. The effects of cheiroarthropathy and of duration of diabetes on skin thickness were examined using multiple regression.

Both the men and women with diabetes of long duration had significantly thicker skin compared with the patients with diabetes of short duration ($p<0{\cdot}001$) and normal controls ($p<0{\cdot}001$) (table). The skin was also significantly thicker in the men with diabetes of short duration compared with the normal controls ($p<0{\cdot}01$) and, after allowance was made for duration of disease, in the male diabetics with cheiroarthropathy compared with those without ($p<0{\cdot}01$). The women with diabetes were not examined for cheiroarthropathy as there were too few for statistical analysis.

Comment

Ultrasound A scanning is an accurate and non-invasive technique for measuring thickness of the skin, giving reproducible results.[3] With this technique skin was shown to be thicker in male and female insulin dependent diabetics. Thickness also increased with duration of diabetes and in men was closely related to cheiroarthropathy.

The pathogenesis of the increased skin thickness is uncertain. There are several reports of defects in connective tissue in patients with diabetes mellitus. It has been suggested that once secreted, collagen is slowly glycosylated, initially reversibly, and then undergoes an irreversible Amadori rearrangement. Further glycosylation results in the accumulation of end products that increase cross linkage of collagen and decrease its susceptibility to in vivo proteolysis. Alternatively, other mechanisms that alter the synthesis, deposition, and catabolism of collagen might contribute to the thicker skin observed in the diabetics of long standing in our study[5] and underlie similar changes in connective tissue at other sites such as periarticular tissue, resulting in cheiroarthropathy. Whether such changes in subcutaneous tissue affect the kinetics of absorption of insulin and whether abnormalities of collagen play a part in other complications of diabetes remain unresolved.

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Mean (SD) skin thickness in normal and diabetic subjects

	Men			Women		
	No	Age (years)	Skin thickness (μm)	No	Age (years)	Skin thickness (μm)
Normal subjects	20	27·3 (4·4)	1073 (110)	20	27·9 (4·7)	918 (91)
Patients with diabetes:						
Of short duration (<18 months)	16	27·5 (6·7)	1183 (92)	10	25·7 (4·1)	974 (101)
Of long duration (>10 years)	48	29·5 (5·7)	1396 (167)	18	26·9 (5·1)	1186 (144)
With cheiroarthropathy*	17	30·5 (6·1)	1522 (160)			
Without cheiroarthropathy†	31	28·5 (4·9)	1326 (168)			

*Mean duration of diabetes 17·9 (4·9) years.
†Mean duration of diabetes 13·2 (4·2) years.