many years (more than 10 years in some cases). Given the variation in sesquiterpene lactone content between varieties of feverfew and plants harvested in different seasons (P J Hylands, unpublished findings), it would seem desirable for commercial preparations of feverfew to be standardised chemically.

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SHORT REPORTS

Plasminogen activator inhibitor in the blood of patients with coronary artery disease

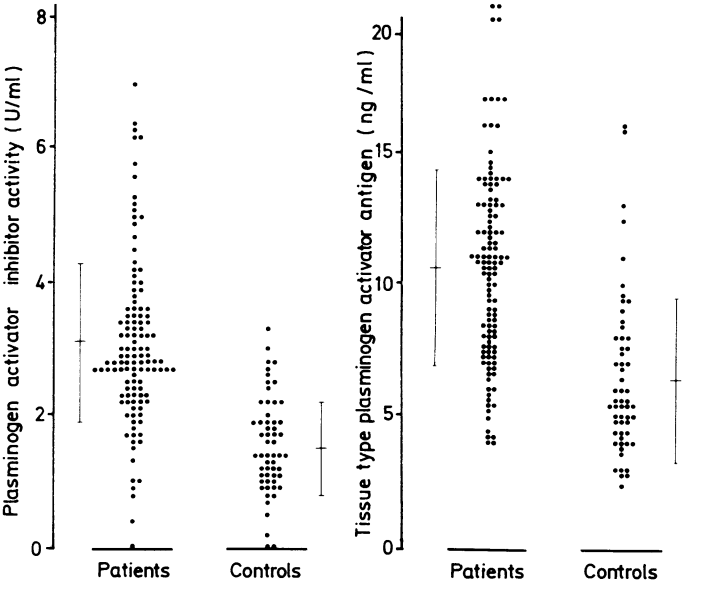
Impairment of fibrinolytic activity in blood has been claimed to contribute to the development of coronary artery disease and myocardial infarction.[1] Human plasma contains a fast acting inhibitor of tissue type plasminogen activator, which may have a primary role in the regulation of the fibrinolytic system.[2] Increased activity of this plasminogen activator inhibitor has been found in clinical and experimental conditions associated with reduced fibrinolytic activity and thrombotic phenomena.[3 4] We studied the activity of plasminogen activator inhibitor in the plasma of patients with angiographic evidence of coronary artery disease.

Patients, methods, and results

We studied 118 patients (92 men and 26 women, aged 35-70) with angina pectoris who were admitted for coronary angiography and in whom stenosis of the coronary artery was documented. Coronary angiograms were evaluated using a computer assisted reporting system.[5] An overall score of the severity of the coronary lesions was calculated, which took into account the graded narrowing, length, number, and site of the different stenoses. On the basis of this evaluation three patient groups were distinguished: patients with slight coronary lesions (coronary severity score <25; $n=45$); patients with moderate lesions (coronary severity score 26-50; $n=50$); and patients with severe lesions (coronary severity score >50; $n=23$). Twenty six patients were taking β adrenergic blockers at the time of angiographic evaluation. Blood samples were collected on trisodium citrate (0·011M final concentration) on arrival at the hospital. Plasma was immediately prepared by centrifugation (20 minutes at 1500 *g*) and stored at −70°C. A control group matched for age consisting of 57 apparently healthy subjects (31 men and 26 women, aged 40-64) was studied simultaneously. Plasma euglobulin fibrinolytic activity was measured with the fibrin plate method, tissue type plasminogen activator related antigen by a two site immunoradiometric assay, and activity of plasminogen activator inhibitor with an amidolytic assay.[4]

Significantly increased activity of plasminogen activator inhibitor (3·1 (SD 1·2) U/ml *v* 1·5 (0·7) U/ml, $p<0·001$) and concentrations of tissue type plasminogen activator antigen (10·6 (3·7) ng/ml *v* 6·4 (3·1) ng/ml, $p<0·001$) were found in the patients compared with the controls (figure); plasma euglobulin fibrinolytic activity was, however, not significantly different (0·8 (0·3) IU/ml *v* 0·9 (0·2) IU/ml). The activity of plasminogen activator inhibitor and concentration of tissue type plasminogen activator antigen were not significantly different in the three groups of patients with different degrees of coronary lesions.

No correlation was found between plasma activity of plasminogen activator inhibitor and either the concentration of tissue type plasminogen activator antigen or the euglobulin fibrinolytic activity. Plasminogen activator inhibitor activity did not correlate with cholesterol and high density lipoprotein cholesterol concentrations and was not different in patients taking β adrenergic blockers. Finally, there was no difference related to sex in the plasminogen activator inhibitor activity or the concentration of tissue type plasminogen activator antigen either in the patients (3·0 (1·3) U/ml in men *v* 3·3 (1·2) U/ml in women, and 10·7 (3·8) ng/ml *v* 9·8 (3·2) ng/ml) or in the controls (1·5 (0·7) U/ml *v* 1·5 (0·7) U/ml, and 7·0 (3·0) ng/ml *v* 6·0 (3·1) ng/ml).



Activity of plasminogen activator inhibitor (left) and concentration of tissue type plasminogen activator antigen (right) in plasma of patients with coronary artery disease and controls. Means (and SD) are shown.

Comment

Our findings suggest that the fibrinolytic system is altered in patients with coronary artery disease. In particular, the functional levels of the fast acting inhibitor of plasminogen activator are significantly increased. The observations that the overall euglobulin fibrinolytic activity is similar in patients and controls and does not correlate with the plasma plasminogen activator inhibitor activity are not totally surprising. The euglobulin fraction, indeed, contains other plasminogen activators different from tissue type plasminogen activator (and not neutralised by plasminogen activator inhibitor), which may represent more than 90% of the total activity and, most probably, do not have an important role in the activation of the fibrinolytic system in vivo.

The increased activity of plasminogen activator inhibitor in the plasma of patients with coronary artery disease may contribute to the impairment of the fibrinolytic capacity and thus represent another risk factor worthy of consideration in the disease.

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Plasma testosterone concentrations in asthmatic men treated with glucocorticoids

Patients receiving pharmacological doses of glucocorticoids may develop several complications secondary to the drugs' catabolic effects on bone, muscle, and skin. Hypogonadism may induce similar changes and contribute to the damage induced by glucocorticoids as plasma testosterone concentrations in men are suppressed by the acute administration of glucocorticoids.[1] There is, however, no information on pituitary and gonadal function in men who are treated with long term glucocorticoids. We examined this issue in asthmatic patients dependent on steroids.

Patients, methods, and results

Eleven asthmatic men requiring continuous treatment with prednisone in daily doses greater than 7·5 mg were matched by age with asthmatic patients who were not receiving glucocorticoids. The mean (SEM) prednisone dose was 17·6 (2·9) mg/day and the mean (SEM) duration of treatment 6·9 (1·8) years. The mean ages of patients in the glucocorticoid and control groups were 55·4 years (range 24-74) and 54·7 years (range 21-77), respectively. All subjects were studied in the outpatient clinic and were free from acute symptoms of asthma. Blood samples were taken mid-morning for measurement of total testosterone, dehydroepiandrosterone sulphate, sex hormone binding globulin, follicle stimulating hormone, and luteinising hormone concentrations. Blood for measurement of zinc concentrations was drawn, with minimal venostasis, into plastic tubes containing heparin free from zinc.

Testosterone and dehydroepiandrosterone sulphate concentrations were measured by in house radioimmunoassays with highly specific antisera and gonadotrophins by Amerlex RIA kits. Sex hormone binding globulin concentration was measured by the method of Rudd *et al*[2] and used, with total testosterone concentrations, to derive plasma free testosterone concentration. Plasma zinc concentration was measured by atomic absorption spectrometry. Comparisons were made with the Student's *t* test for paired data.

Mean values for plasma total and free testosterone concentrations in the patients treated with glucocorticoids were roughly 60% of those in the control group, and in six patients the concentrations of both were below the normal range (table). In the glucocorticoid group the mean dehydroepiandrosterone sulphate concentration was 26% of that of the control group, and plasma follicle stimulating hormone and luteinising hormone concentrations were higher by 52% and 100%, respectively. Plasma zinc concentrations did not differ between the groups.

Plasma biochemical variables of asthmatic men treated with glucocorticoids and matched for age asthmatic controls. Values are means (SEM) (and normal ranges)

	Treatment group		
	Control (n = 11)	Glucocorticoid (n = 11)	p Value
Total testosterone (nmol/l)	19·4 (1·2)	12·2 (1·7) (13-40)	<0·01
Sex hormone binding globulin (nmol/l)	54·9 (2·7)	53·6 (2·2) (40-65)	NS
Calculated free testosterone (pmol/l)	578 (54)	340 (49) (380-1200)	<0·01
Follicle stimulating hormone (mIU/ml)	6·5 (0·9)	9·9 (1·2) (1-9)	<0·02
Luteinising hormone (mIU/ml)	8·2 (1·1)	16·5 (3·6) (2-12)	<0·05
Dehydroepiandrosterone sulphate (μmol/l)	3·2 (1·1)	0·9 (0·2) (2-10)	<0·05
Zinc* (μmol/l)	11·6 (0·3)	11·1 (0·5) (12-20)	NS

*Measured in 10 pairs of subjects only.
Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 0·3 ng/ml. Dehydroepiandrosterone sulphate: 1 μmol/l ≈ 0·367 μg/ml. Zinc: 1 μmol/l ≈ 0·07 mg/l.

Comment

These data show that long term administration of prednisone to asthmatic men suppresses plasma testosterone concentrations. The raised plasma follicle stimulating hormone and luteinising hormone concentrations indicate an appropriate pituitary response and suggest either a direct action of the glucocorticoid on synthesis of testosterone or a reduction in the supply of substrate, such as adrenal dehydroepiandrosterone, to the testis. A direct action on the testis seems more probable as the increase in plasma cortisol concentration that follows administration of corticotrophin is also accompanied by a decrease in plasma testosterone concentration.[11]

The nature of the testicular defect is unclear. Deficiency in zinc has been described in asthmatic patients treated with glucocorticoids[3] and is a recognised cause of hypogonadism. This is unlikely to be the mechanism in our study as plasma zinc concentrations were the same in each group. Studies in rats have suggested that glucocorticoids may reduce the number of gonadotrophin binding sites on testicular cells,[4] and our data are consistent with such a mechanism.

In men testosterone is thought to promote formation of bone, inhibit resorption of bone, and thus lead to positive balance of calcium.[5] The major reduction in plasma testosterone concentration seen in these patients might therefore contribute appreciably to the development of osteoporosis and also to the soft tissue atrophy associated with the use of glucocorticoids. As established osteoporosis induced by glucocorticoids is a difficult clinical problem plasma testosterone concentrations should be measured in all men receiving long term treatment with glucocorticoids and replacement treatment given if low concentrations are found.

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Correction

Importance of hypovolaemic shock and endoscopic signs in predicting recurrent haemorrhage from peptic ulceration: a prospective evaluation

Three errors occurred in this paper by P C Bornman *et al* (27 July, p 245). In table I the number of rebleeds in patients with endoscopic signs of a clot should have read 12 (25) not 11 (23). In table II the value 112 under "No endoscopic sign, black spots" should have read 86, and the remaining 26 patients should have been tabulated under "Endoscopic sign, no rebleed."