clofibrate showed an increase in sex-hormone-binding capacity (11·9 and 7·5 × 10⁻⁸ mol/l in cases and controls respectively) and a decrease in the percentage of testosterone circulating free in the unbound state (1·1% and 1·6% respectively), both differences being statistically significant (p < 0·05). Though total testosterone was higher and oestrone and oestradiol lower in those taking clofibrate than in their controls, the differences were not significant. Comparison of men not taking medication with their matched controls showed a non-significant increase in total testosterone, oestrone, and oestradiol. When the hormone concentrations were put into a multiple
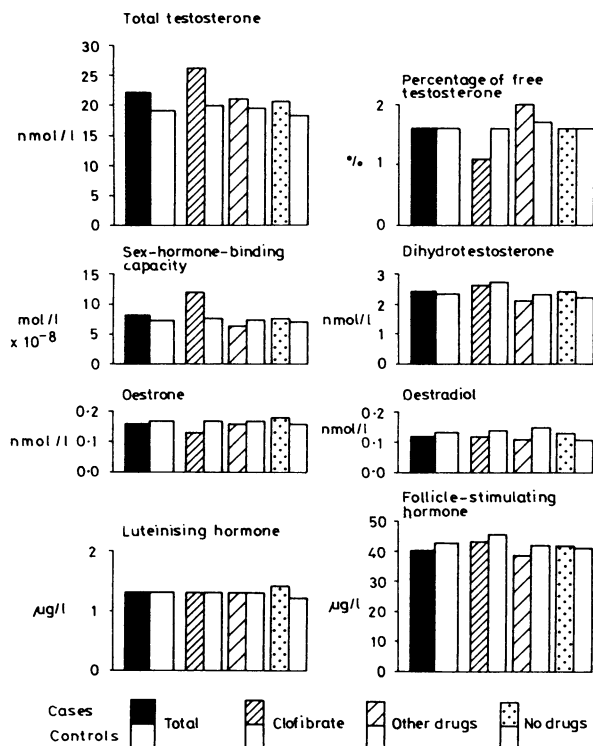
Hormone concentrations in cases, grouped according to current drug treatment, compared with their matched control pairs. Numbers of pairs (total = 50): clofibrate, 12; other drugs, 16; no drugs, 22. (One value missing for each of % free testosterone, sex-hormone-binding capacity, oestradiol, luteinising hormone and follicle-stimulating hormone; 11 values missing for oestrone; 16 values missing for dihydrotestosterone.)

Conversion: SI to traditional units—Testosterone: 1 nmol/l ≈ 28·8 ng/100 ml. Oestrone: 1 nmol/l ≈ 27 ng/100 ml. Dihydrotestosterone: 1 nmol/l ≈ 29 ng/100 ml. Oestradiol: 1 nmol/l ≈ 27·2 ng/100 ml.

linear regression model (to examine case-control differences while taking account of the effect of drugs and other risk factors for coronary heart disease) testosterone was a better discriminator between cases and controls (t = 1·78; p < 0·10) than either oestrone or oestradiol, but none of these hormonal differences were statistically significant.

Comment

Although the patients in this study were survivors of myocardial infarction and may thus have been somewhat unrepresentative of all men with coronary heart disease, they were particularly well matched with the controls: the members of each pair were working in the same factory, were of the same age and marital state, and had blood taken at the same time of day under identical conditions. A major effect of clofibrate on sex hormones had not, however, been anticipated and seriously influenced the case-control comparisons. The primary mechanism is probably an increase in sex-hormone-binding globulin, which reduces the proportion of testosterone circulating in the free unbound state, an effect which mimics the known influence of clofibrate on thyroid hormone metabolism, where it has been shown to increase thyroxine-binding globulin and decrease the percentage of free thyroxine.[3]

Our results do not show any significant excess of sex hormone concentrations in men with coronary heart disease and suggest that if there is a difference it is probably on the testosterone rather than the oestrogen side: we do not confirm reports of much higher plasma oestrogen concentrations in men with coronary heart disease than in controls.[4][5]

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Fetal macrosomia and maternal diabetic control in pregnancy

Infants of diabetic mothers tend to have more adipose tissue than normal at birth, and the associated macrosomia is an important complication of diabetic pregnancy. Subcutaneous fat as assessed by neonatal skinfold thickness correlates with maternal blood glucose concentrations in the third trimester of pregnancy,[1] but the contribution of maternal hyperglycaemia earlier in pregnancy is uncertain.

To determine the possible role of maternal hyperglycaemia at earlier stages of pregnancy in subsequent fetal macrosomia we correlated maternal glycosylated haemoglobin (HbA₁) and blood glucose concentrations measured in all three trimesters of pregnancy with the neonatal birth weight and skinfold thickness.

Methods and results

We studied 43 insulin-dependent diabetics. All delivered normal live healthy babies at 36-38 weeks' gestation. HbA₁ was measured blind and in duplicate[2] on presentation to the antenatal clinic, at delivery, and usually at one other time during pregnancy. Gestational age was divided into three periods—namely, 14 weeks and under, 15-27 weeks, and 28 weeks and over. When HbA₁ concentration had been measured more than once in a single period the mean value was taken. Random blood glucose concentrations were measured in all patients as outpatients at intervals of two to four weeks throughout pregnancy. After routine admission to hospital at 30-34 weeks preprandial blood glucose concentration was measured twice weekly. Birth weight was recorded and the birthweight ratio calculated as the ratio between the birth weight and the 50th percentile weight for that gestational age.[3] Skinfold thickness was measured using a Holtain skin callipers within 12-36 hours of delivery.[2] The sum of the readings from the biceps, triceps, subscapular, and sacroiliac sites on the left and right was recorded. Statistical analysis was made using Pearson's regression analysis. Values of p < 0·05 were accepted as significant.

Concentrations of HbA₁ fell from 9·6 ± SD 2·0% in the first trimester to 8·8 ± 1·5% in the second and 7·9 ± 1·3% in the third (p < 0·001 between first and third trimesters, p < 0·02 between second and third trimesters). HbA₁ concentrations at delivery and during the third trimester were correlated with the mean inpatient blood glucose concentration between 32 and 38 weeks' gestation (r = 0·32, p < 0·05). The neonatal total skinfold thickness correlated with the mean HbA₁ concentrations in the third trimester (r = 0·52,

Correlation coefficients (r) between HbA₁ concentrations at each period of gestation and at delivery and total skinfold thickness, birth weight, and birth-weight ratio

	Weeks of gestation						Delivery	
	≤14		15-27		≥28			
	No	r	No	r	No	r	No	r
Total skinfold thickness	17	0·38	14	0·26	38	0·52†	25	0·46*
Birth weight	19	0·28	15	−0·12	42	0·25	28	0·17
Birthweight ratio	19	0·26	15	−0·09	42	0·28	28	0·20
Mean ±SD HbA₁ (%)	9·6±2·0		8·8±1·5		7·9±1·3		8·1±1·1	

†p<0·001.
*p<0·05.

p <0·001) and at delivery (r=0·46, p<0·05) (table), and with the mean in-patient blood glucose concentration (r=0·42, p<0·01).

The mean inpatient blood glucose concentration but not the HbA₁ concentration correlated with the birthweight ratio (r=0·30, p<0·05). Neither HbA₁ nor mean inpatient blood glucose concentrations correlated with the birth weight. There was no correlation between the HbA₁ or the mean outpatient blood glucose concentrations in the first and second trimesters and the total skinfold thickness, birth weight, or birthweight ratio.

Comment

Maternal diabetic control in the third trimester, whether estimated by HbA₁ or mean blood glucose concentrations, was related to the amount of neonatal subcutaneous fat. No relation was found between diabetic control in the first and second trimesters and skinfold thickness, birthweight ratio, or birth weight. These observations suggest that subcutaneous fat in the infants of diabetic mothers is determined by control of maternal blood glucose in the third trimester.

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Pulmonary eosinophilia and asthma associated with carbamazepine

Carbamazepine (Tegretol) is the medical treatment of choice for trigeminal neuralgia and is used in many cases of temporal lobe epilepsy. Although phenytoin has often been associated with pulmon-ary abnormalities, pulmonary complications with carbamazepine are rarely recognised. We describe a case of pulmonary eosinophilia and asthma believed to have been caused by carbamazepine.

Case report

A 52-year-old man presented with a two-month history of an itchy rash on his legs and a month's history of asthma, which had been partially relieved with antihistamines. He had also suffered from trigeminal neuralgia for nine months, for which he was taking carbamazepine 200 mg three times daily. On examination he was mildly feverish, wheezy, and had discoid eczema on his limbs. He had moderate airflow obstruction, forced expiratory volume in 1 second was 1·0 l (predicted 3·2 l), forced vital capacity was 2·0 l (4·2 l), and forced expiratory ratio was 50% (76%) with a normal carbon monoxide transfer coefficient. Chest x-ray examination showed a left apical segmental shadow, a blood count showed a 20% eosinophilia (1·9 × 10⁹/l), and erythro-cyte sedimentation rate was 40 mm in first hour. There were eosinophils in his sputum but renal and liver function were normal. Repeated examinations of his sputum, stools, and blood showed no bacterial, fungal, or parasitic infection. Prick tests to common allergens, aspergillus and candida were negative despite a positive histamine control. Tests using precipitins to aspergillus and candida were negative. The concentration of serum IgE was raised at 250 U/ml (normal: <122 U/ml) but other immunoglobulin concentrations were normal.

His asthma deteriorated considerably over 48 hours when his anti-histamines were stopped, and these were reinstituted with nebulised salbutamol before there was clinical improvement. Carbamazepine was stopped and within 72 hours his peripheral eosinophil count, erythrocyte sedimentation rate, and chest radiograph were normal. The rash disappeared within three days but his asthma remained troublesome for six months before complete recovery, despite a good initial response to a short course of prednisolone.

Unfortunately his trigeminal neuralgia was poorly controlled with pheny-toin, so to prove that he did have carbamazepine sensitivity, he was chal-lenged with 200 mg carbamazepine. A mild eczematous rash appeared after six hours but there was no airflow obstruction or radiological abnormalities, although there was a slight increase in his eosinophil count from 3% to 5% over this time. Carbamazepine was continued under close supervision and over the next two weeks cusum analysis¹ showed that his asthma had gradu-ally deteriorated. This improved again when the drug was discontinued. A positive lymphocyte stimulation assay (stimulation index >2) to carbamaze-pine was maximal at 1 mg/l of the drug in the presence of autologous serum; the stimulation index was 3·26 (index of positive control to 10 mg/l purified protein derivative was 14·4). Such a pronounced response on lymphocyte stimulation supported the role of carbamazepine as the cause of his symptoms.

Comment

Unlike our case, two previous cases of acute pulmonary reactions associated with carbamazepine treatment² ³ were complicated by tuberculosis² and Mycoplasma pneumoniae infection. Nevertheless, their clinical pictures suggested that carbamazepine hypersensitivity was indeed a problem. The presymptomatic exposure to carbamaze-pine varied; the patients had been taking the drug for five weeks, three months, and, in our case, nine months before presentation. All patients presented with a rash and eosinophilia with their pulmonary disease. The total duration of their illnesses also varied greatly and, although one patient recovered within nine days,³ the other took five weeks,² and our patient took six months to recover completely. The treatment is supportive but the drug must be stopped. The use of corticosteroids is dictated by the patient's condition, although the patient would probably recover without them.

The mechanism for this complication is unknown and the pro-nounced deterioration of our patient's asthma after the withdrawal of antihistamines is interesting. Lymphocyte transformation in the presence of carbamazepine has been reported² ⁴ and is similar to that found in nitrofurantoin sensitivity, which is better documented as a cause of pulmonary eosinophilia. The pathogenesis of the pulmonary eosinophilia in nitrofurantoin sensitivity is thought to include not only T-lymphocytes but also immune complexes formed between the drug and antibody.⁵

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