size was thought to be in the upper-normal range. Testicular volume remained 1-2 ml.

At 15 months plasma diurnal cortisol concentrations were normal. A combined insulin hypoglycaemia test for growth hormone and cortisol and tests for thyrotrophin-releasing hormone and luteinising hormone-releasing hormone gave normal results, basal concentrations of luteinising and follicle-stimulating hormones being 2.1 and <0.4 U/l respectively. Basal thyroxine, triiodothyronine, and prolactin concentrations were normal. Urinary free cortisol, plasma 17 α -hydroxyprogesterone, dehydroepiandrosterone sulphate, and androstenedione; 24-hour urinary 17-oxosteroids, 17-oxogenic steroids, and 17-hydroxycorticosteroids; and ultrasound

Acne on infant's face.

examination of the adrenals and intravenous pyelography were normal. The pituitary fossa on skull x-ray examination was thought to be of omega type, a normal variant. Plasma testosterone concentration was 2.4 nmol/l (692 pg/ml) (normal 0.23 $\pm$ SD 0.09 nmol/l (66 $\pm$ 26 pg/ml) at that age.¹

He was followed up and continued to thrive, though his acne persisted. At 26 months the acne was much improved, examination was otherwise normal, and a random plasma testosterone concentration was <0.5 nmol/l (144 pg/ml).

Comment

Infantile acne is rare. Several drugs may cause acne but none were ingested by this patient. Exceptionally, infantile acne may be associated with an excess of androgens—for example, in Cushing's syndrome. Bessone² studied over 60 patients with infantile acne (80% being boys) and found that the onset was usually in the first 12 months. Virtually all subjects showed no evidence of other androgenic abnormalities, but many had an abnormally high excretion of 17-ketogenic steroids. Infantile acne often lasts until the age of 3 or 4 years but may persist longer.³

A normal boy has a neonatal rise in plasma concentrations of luteinising and follicle-stimulating hormones lasting for three to four months⁴ and associated with a transient rise in plasma testosterone to a peak at 1 month in the low adult range (mean peak values 9.3 $\pm$ 1.1 nmol/l (2682 $\pm$ 317 pg/ml)).¹ This returns to normal prepubertal values by 7 months (0.25 $\pm$ 0.14 nmol/l (72 $\pm$ 40 pg/ml)).

Investigations showed no cause for the transient abnormalities in hormone concentrations in this boy. The hypothalamopituitary-gonadal negative feedback mechanism functions at this age, and the prepubertal hypothalamic "gonadostat"⁵ (the sensitivity of the feedback mechanism) appears to mature from birth, when it has a high threshold of sensitivity, to become set at a low threshold of sensitivity from 7 months until shortly before puberty, when it alters again to have a high threshold of sensitivity.¹ Possibly this patient had a prolonged period of immaturity of the gonadostat with a high threshold of sensitivity. The findings are similar to those in isolated premature thelarche,⁵ when transient increases in plasma luteinising and follicle-stimulating hormones and 17 β -oestradiol are found. I suggest that similar studies should be done on a group of infants with acne to see whether these findings are unique or a common mechanism.

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Enterotoxigenic effect of methotrexate: does it influence the drug's absorption in children with acute lymphoblastic leukaemia?

Xylose malabsorption occurs in children with acute lymphoblastic leukaemia receiving methotrexate maintenance treatment,¹ and it has been suggested that either an acute² or a cumulative³ toxic effect on the small gut may be associated with the drug's malabsorption. We studied the relation between absorption of methotrexate and xylose and both the standard five-day oral course of methotrexate (acute effect) and a prolonged period of maintenance treatment (cumulative effect).

Patients, methods, and results

We studied 32 children aged 3-15 (mean 7.1) years with acute lymphoblastic leukaemia: all were in remission being treated according to a UKALL trial protocol, most taking either a single weekly dose of methotrexate or a five-day course every three or four weeks. After an overnight fast a venous

Mean ($\pm$ SEM) methotrexate absorption profiles and blood xylose concentrations in eight patients on first and fifth days of a course of methotrexate and in nine patients receiving regular methotrexate studied at an interval

	Peak methotrexate concentration (μ mol/l)	Time of peak concentration (hours)	Rate of absorption (μ mol/h)	Area under curve (μ mol h/l)	One-hour blood xylose (mmol/l)
<i>Patients receiving five-day course</i>					
Day 1	0.89 $\pm$ 0.10	1.8 $\pm$ 0.3	0.83 $\pm$ 0.15	2.2 $\pm$ 0.4	0.9 $\pm$ 0.1
Day 5	0.93 $\pm$ 0.11	1.5 $\pm$ 0.1	0.85 $\pm$ 0.15	2.2 $\pm$ 0.2	1.1 $\pm$ 0.1
<i>Patients receiving maintenance treatment</i>					
First study	0.90 $\pm$ 0.16	1.8 $\pm$ 0.2	0.75 $\pm$ 0.16	1.6 $\pm$ 0.3	1.2 $\pm$ 0.2
Repeat study	0.96 $\pm$ 0.12	1.6 $\pm$ 0.3	0.92 $\pm$ 0.18	2.2 $\pm$ 0.5	1.0 $\pm$ 0.2

Conversion: SI to traditional units—Methotrexate: 1 μ mol/l $\approx$ 45.4 μ g/100 ml. Xylose: 1 mmol/l $\approx$ 15 mg/100 ml.

cannula was inserted and a resting blood sample withdrawn. Methotrexate (15 mg/m²) was given with water, and further samples were obtained at 20, 40, 60, and 90 minutes and at two, three, and four hours. Serum was separated and stored at -20°C until analysed by immunoassay (Emit, Maidenhead) within two weeks. The "blood xylose concentration" was the difference between the resting value and that one hour after 5 g of D-xylose was given in 50 ml water.

Eight patients were studied on the first and fifth days of a five-day course of Methotrexate (table); of the remaining 24 patients, seven were studied before the start of maintenance treatment; five at least six months after completion of treatment; and 12 while taking methotrexate for between one and 96 (mean 27.7) months. Nine of these 12 were studied twice at an interval varying from two to five months (table). Serum methotrexate profiles were analysed to determine the peak concentration, peak time, rate of absorption (from the linear gradient of the absorption phase plot), and area under the serum concentration curve (trapezoid method).

The study protocol was approved by the ethical committee of The Queen's University of Belfast.

Paired *t*-test analysis of the data on the first eight patients showed no significant differences between either the features of the methotrexate absorption profile or the blood xylose concentration on the first, as compared with the fifth, day of the course of treatment. In the group as a whole (32 patients), there was no correlation between peak concentration, peak time, rate of absorption, or area under the curve and the duration of treatment, the total dose of methotrexate, or whether the drug was given weekly or over five days. Blood xylose concentration (mean $\pm$ SEM) in patients receiving methotrexate was significantly lower (0.75 ± 0.12 mmol/l (11.3 ± 1.8 mg/100 ml)) than in those who were not receiving the drug (1.6 ± 0.05 mmol/l (24.0 ± 0.8 mg/100 ml)) ($p < 0.001$); those who received methotrexate weekly had a significantly lower xylose concentration (0.57 ± 0.10 mmol/l (8.6 ± 1.5 mg/100 ml)) compared with those receiving a five-day course every three to four weeks (0.95 ± 0.11 mmol/l (14.3 ± 1.7 mg/100 ml)) ($p < 0.05$). There was no correlation between either duration of methotrexate treatment or its cumulative dose and blood xylose concentration. Neither the peak methotrexate concentration nor the area under the curve correlated with the blood xylose concentration. In the nine patients studied twice neither the features of the methotrexate absorption profiles nor blood xylose concentration altered significantly.

Comment

Poor absorption of methotrexate in some children with acute lymphoblastic leukaemia under fasting conditions has been clearly shown.⁴ Our data show, however, that xylose absorption should not be used to predict methotrexate absorption since peak concentrations and the area under the curve may be high in the presence of significantly reduced xylose absorption.

Histological abnormalities in the jejunum have been reported during treatment with methotrexate,⁵ but, unlike the grosser lesions induced in animals by high or prolonged doses, such changes do not cause a reduction in jejunal transport of methotrexate. By contrast, concentrations of xylose, which is also actively absorbed, remained abnormal as long as patients were taking the drug.

Clearly, these data do not suggest that the route of administering methotrexate be altered, either during a five-day course or after prolonged treatment, on the basis of drug-induced malabsorption.

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Cardiovascular disease and hormone replacement treatment: a pilot case-control study

Many epidemiological studies have shown a relation between the use of oestrogen-progestogen oral contraceptives and the risk of certain cardiovascular diseases—notably, venous thromboembolism, stroke, and acute myocardial infarction.¹ Similar studies of the possible association between hormone replacement treatment in older women and cardiovascular disease are, however, relatively few and all have been conducted in the United States.^{1,2} Accordingly, we undertook a pilot case-control study of deaths from acute myocardial infarction and subarachnoid haemorrhage in middle-aged women.

Patients, methods, and results

We obtained all 248 death certificates relating to women aged 50-59 who died in England and Wales during November 1978 and in whom the cause of death was stated to be acute myocardial infarction or subarachnoid haemorrhage. An attempt was made to obtain copies of relevant hospital records and postmortem reports and also to identify the general practitioner who had been responsible for the medical care of each patient during life. As a result of these efforts 33 cases were excluded from the study either because the diagnosis was incorrect or unsupported or because acute myocardial infarction or subarachnoid haemorrhage had been a terminal event in a longstanding chronic disease. A further 25 cases could not be traced. We wrote to the general practitioners who had cared for the remaining 190 women asking them to complete a simple questionnaire (on the basis of information in the medical records) both for the woman who had died and

Characteristics of women who died as a result of acute myocardial infarction (AMI) or subarachnoid haemorrhage (SAH) and of their controls. Results are numbers (%) of patients

	AMI (n = 76)	Controls (n = 151)	SAH (n = 23)	Controls (n = 45)
History of:				
Angina	19 (25)	2 (1)	0	0
Acute myocardial infarction	13 (17)	0	0	0
Stroke	9 (12)	2 (1)	2 (9)	0
Diabetes	7 (9)	2 (1)	0	0
Toxaemia	6 (8)	5 (3)	1 (4)	3 (7)
Hypertension	27 (36)	17 (11)	8 (35)	7 (16)
Hyperlipidaemia	4 (5)	2 (1)	0	0
Known to have had hysterectomy	8 (11)	15 (10)	4 (17)	5 (11)
Smoking habits:				
Smokers	22 (29)	20 (13)	7 (30)	2 (4)
Non-smokers	16 (21)	38 (25)	4 (17)	7 (16)
Unknown	38 (50)	93 (62)	12 (52)	36 (80)
Received hormone replacement treatment:				
At any time	9 (12)	26 (17)	1 (4)	3 (7)
At time of subject's death	2 (3)	5 (3)	0	0
For more than two years	1 (1)	5 (3)	0	1 (2)
For more than four years	1 (1)	2 (1)	0	1 (2)

for two control subjects on the practice list, randomly selected by a defined procedure and matched for age. Questions were asked about medical history, smoking habits, hormone replacement treatment, and menopausal status. Fully completed questionnaires were received from 97 general practitioners; two provided information about the case and only one control, seven provided data about the case alone, while 84 failed to respond at all despite three requests by mail. No attempt was made to contact the general practitioners by telephone or in person as this was a pilot study. The following analysis relates only to the 76 cases of acute myocardial infarction and 23 cases of subarachnoid haemorrhage for whom control data were also obtained.

The table shows that the women who died from acute myocardial infarction more often had a history of angina, previous acute myocardial infarction, stroke, diabetes, toxaemia, hypertension, hyperlipidaemia, and tobacco smoking than their controls. Hormone replacement treatment was uncommon in both groups of women, especially prolonged treatment, and only 3% of both cases and controls were receiving hormone replacement treatment at the time of the subject's death. Unexpectedly, there was little association between the presence of risk factors for acute myocardial infarction and use of hormone replacement treatment. Restricting the analysis of hormone replacement treatment to cases and controls without risk factors therefore produced results that were similar to those shown in the table.

Women whose death was caused by subarachnoid haemorrhage more often had a history of stroke, hypertension, and tobacco smoking than their controls. Only one case and three controls had ever received hormone replacement treatment.