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.

We thank Mr H Mackey and Mr M McMaster, Belfast City Hospital; Mr T Macfarlane and the staff of the biochemistry and haematology laboratories of the Royal Belfast Hospital for Sick Children for technical help; and Ms L Thompson and Ms J Elliott for secretarial help.

CRP is in receipt of a Royal Belfast Hospital for Sick Children Clinical Research Fellowship.

¹ Craft AW, Kay HEM, Lawson DN, McElwain TJ. Methotrexate-induced malabsorption in children with acute lymphoblastic leukaemia. *Br Med J* 1977;iii:1511-12.

² Smith DK, Omura GA, Ostroy F. Clinical pharmacology of intermediate dose oral methotrexate. *Cancer Chemother Pharmacol* 1980;4:117-20.

³ Calvert AH. Pharmacokinetics of methotrexate and 5 fluorouracil. *Cancer Topics* 1980;2:1-3.

⁴ Kearney PJ, Light PA, Preece A, Mott MG. Unpredictable serum levels after oral methotrexate in children with acute lymphoblastic leukaemia. *Cancer Chemother Pharmacol* 1979;3:117-20.

⁵ Guavava NJT, Pinkerton CR, Glasgow JFT, Sloan JM, Bridges JM. Small bowel enterocyte abnormalities caused by methotrexate therapy in acute lymphoblastic leukaemia of childhood. *J Clin Pathol* (in press).

(Accepted 19 January 1981)

Royal Belfast Hospital for Sick Children, Belfast BT12 6BE

C R PINKERTON, MRCP, DCH, clinical research fellow

The Queen's University of Belfast, Belfast BT12 6BJ

J F T GLASGOW, FRCP, FRCP, senior lecturer department of child health
J M BRIDGES, MD, MRCPATH, professor of haematology

Belfast City Hospital, Belfast BT9 7AB

S G WELSHMAN, PHD, FRIC, top grade biochemist, department of clinical chemistry

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.

Comment

The methods used in this study were reasonably satisfactory, although the response rate from the general practitioners (52%) was rather disappointing.

In common with most other studies,^{1,2} our results provide no evidence of an increase in the risk of cardiovascular disease in women receiving hormone replacement treatment. Nevertheless, few subjects were studied and the use of hormone replacement treatment (especially current use) was generally infrequent. This finding was not unexpected since general practice prescribing data suggest that only about 3% of women aged 45-69 years were using hormone replacement treatment at any given time during the year 1978 (unpublished observations, G T Bungay). It seems doubtful whether a full-scale study of the type we have described would be rewarding unless hormone replacement treatment becomes more widely used.

SAA was supported by a MRC training fellowship in clinical epidemiology. We thank Dr A Adelstein, Office of Population Censuses and Surveys, for supplying the death certificates.

¹ Vessey MP. Female hormones and vascular disease. Epidemiological overview. *British Journal of Family Planning* 1980;6,suppl,1-12.

² Rosenberg L, Slone D, Shapiro S, Kaufman D, Stolley PD, Miettinen OS. Non-contraceptive estrogens and myocardial infarction in young women. *JAMA* 1980;244:339-42.

(Accepted 26 January 1981)

University Department of Community Medicine and General Practice, Oxford OX1 3QN

SHEILA ADAM, MB, MRCP, research fellow

VIVIENNE WILLIAMS, research assistant

M P VESSEY, MD, FRCPD, professor of social and community medicine

Impact of therapeutic audit on phenytoin prescribing

Phenytoin is difficult to use because of its low therapeutic ratio and non-linear kinetics (serum phenytoin concentration increases disproportionately with dose). These problems heighten the risk to epileptic patients, for whom the quality of care is known to be poor.¹ We assessed the effect of a therapeutic audit on the prescribing of phenytoin in one hospital and detected a rapid improvement in prescribing habits.

Methods and results

All adult outpatient prescriptions for phenytoin at this hospital were inspected in 1978 and again in 1980. Information regarding the dose, dosage interval, and incidence of polypharmacy was noted. In 1978 there were 189 scripts for phenytoin; 40% of patients receiving phenytoin were prescribed additional anticonvulsants. There was evidence of underdosing, little fine adjustment of dose, and complicated divided dosage regimens (figure).

In a further study of 229 outpatients in whom phenytoin concentrations were measured between October 1977 and April 1979 evidence of underdosing was supported by low serum concentrations. Frequency of fits was assessed by inspecting the case notes of a representative proportion of these subjects. Fifty out of 81 medical outpatients (62%) reported having had fits since their previous visit, and chronic recurrent seizures were clearly "clinically acceptable."² The implications of these findings were discussed at local clinical meetings and communicated to medical staff.

In 1980 (183 prescriptions) the incidence of polypharmacy was the same (41%). There was a significant increase, however, in phenytoin dosage ($\chi^2 = 80.02$; $p < 0.0001$) and significantly greater use of 25 and 50 mg capsules for fine dosage adjustment ($\chi^2 = 39.62$; $p < 0.0001$). In addition, once- or twice-daily dosing was the rule ($\chi^2 = 139.48$; $p < 0.0001$) rather than the exception. Compared with 1978, serum phenytoin concentrations were more often in the therapeutic range than below it ($n = 147$, $\chi^2 = 3.97$, $p < 0.05$). The proportion of medical outpatients reporting seizures had fallen to 47% ($n = 70$, $\chi^2 = 4.42$, $p < 0.05$).

Comment

The average daily dose required to achieve therapeutic serum phenytoin concentrations of 40-100 $\mu\text{mol/l}$ (10-25 mg/l) is 350-400

mg.³ In an attempt to avoid toxicity underdosing is common and may be associated with poor seizure control,^{1,2} sometimes with disastrous consequences. Small dosage adjustments (25-50 mg) may avoid the risks of toxicity⁴ and may be accompanied by better control, while a simple once-daily regimen⁵ will improve compliance, which is often poor among epileptics. The improvement in seizure control was unassociated with an increase in serum phenytoin monitoring, suggesting that better prescribing, titrated against the frequency of

Percentage of prescriptions for phenytoin related to daily dose, smallest unit dose, and dose interval; and to serum phenytoin concentration.

fits, was largely responsible. Unfortunately, the incidence of polypharmacy did not decline. This is not surprising in view of the difficulty of withdrawing anticonvulsants, the selective nature of the hospital population, and the short time between the two studies. It is important, however, to note the rapid impact of local audit in contrast to the poor response to the glut of publications in this field over the past 20 years.

We thank the physicians of the Royal Hallamshire Hospital for permission to inspect the case notes of patients under their care.

¹ Hopkins A, Scrambler G. How doctors deal with epilepsy. *Lancet* 1977;i:183-6.

² Silas JH, Cawthorne IF. Hospital prescribing of phenytoin for epilepsy. *J R Coll Physicians Lond* 1981;15:41-6.

³ Buchthal F, Svensmark O, Schiller PJ. Clinical and electroencephalographic correlations with serum levels of diphenylhydantoin. *Arch Neurol* 1960;2:624-30.

⁴ Bochner F, Hooper WD, Tyrer JH, Eadie MJ. The effect of dosage increments on blood phenytoin concentrations. *J Neurol Neurosurg Psychiatry* 1972;35:873-6.

⁵ Buchanan RA, Kinkel AW, Goulet JR, Smith TC. The metabolism of diphenylhydantoin following once daily administration. *Neurology* 1972;22:126-30.

(Accepted 4 February 1981)

University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

I F CAWTHORNE, BSC, hospital pharmacist

J H SILAS, MD, MRCP, lecturer