Patients, methods, and results

Twelve patients with cirrhosis (nine men, three women) aged 21-72 years, who were admitted consecutively with bleeding oesophageal varices, were studied three days after the bleeding had stopped. Three of these patients were studied again one month later. The study was approved by the hospital ethics committee. Wedged and free hepatic venous pressure were measured using a Cordis Cobra II torque-controlled balloon catheter, French gauge 7 (Cordis Corporation, Miami, USA), as described by Groszmann *et al.*³ Pressures were also recorded in the right atrium, and in the inferior vena cava within the liver and above and below it. Measurements were made with a Hewlett-Packard 1280 series physiologic pressure transducer linked to a Hewlett-Packard blood-pressure module 78205A. After the patient was settled three recordings of wedged and free hepatic venous pressures were taken over 10 minutes. Cimetidine 200 mg was then given intravenously, and after 10 minutes three more readings of wedged and free hepatic venous pressures were taken over the next 10 minutes.

The figure shows the gradients between wedged and free hepatic venous pressures in each patient before and 10 minutes after 200 mg cimetidine given intravenously. There was no significant difference between the means of the pressure gradients before ($16.8 \pm \text{SD } 4.2$ mm Hg) and after cimetidine (16.1 ± 3.1 mm Hg).

Effect of 200 mg cimetidine given intravenously on gradient between wedged and free hepatic venous pressures, using average of three readings. (*, Δ, □ = Patients studied twice one month apart.)

Comment

In this study of patients with cirrhosis 200 mg cimetidine given intravenously did not reduce portal hypertension as measured by the gradient between wedged and free hepatic venous pressures. The dose of cimetidine used is unlikely to have been insufficient to produce a reduction in portal pressure, since the same dose saturates H_2 -receptors in the systemic circulation within minutes.⁴ This largely removes the proposed rationale for long-term use of cimetidine to prevent recurrent variceal haemorrhage. Prospective trials of cimetidine prophylaxis are likely to be disappointing.

As cimetidine does not affect portal pressure in patients with cirrhosis it probably does not reduce splanchnic blood flow. The possibility that it causes simultaneous vasoconstriction in the portal system to maintain portal pressure is highly unlikely. The original report¹ that cimetidine reduces blood flow to the liver in normal subjects has itself been challenged. In that study hepatic blood flow was measured by clearance of indocyanine green and the reduction after cimetidine interpreted as indicating decreased liver blood flow. The reduction in indocyanine green clearance after cimetidine may, however, have been caused not only by a decrease in blood flow to the liver but also by a decrease in extraction of indocyanine green. Such a decrease in extraction of indocyanine green after cimetidine has been shown in two patients with liver disease, in whom hepatic blood flow apparently increased.⁵ This provides further support for our conclusion that cimetidine does not have any effect on portal hypertension in patients with cirrhosis and so is unlikely to be beneficial in preventing recurrent bleeding from gastrooesophageal varices.

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Cyclophosphamide treatment of systemic lupus erythematosus: risk of bladder cancer exceeds benefit

Systemic lupus erythematosus has a variable clinical course, making assessment of treatment difficult. In association with steroids cyclophosphamide has been used to treat the disease for at least 20 years. Cyclophosphamide is claimed to reduce the dose of steroids required but is extremely toxic.

We report on two women who developed bladder cancer after prolonged treatment with cyclophosphamide.

Case 1—A 28-year-old woman developed systemic lupus erythematosus in 1969 after exposure to sunlight. Symptoms included rash, haemolytic anaemia, and proteinuria. Renal biopsy specimens showed proliferative glomerulonephritis. Treatment was started with steroids and with cyclophosphamide 50-100 mg daily, which was given intermittently for six years. In 1981 she presented with symptoms of urinary tract infection. Cultures were sterile. Intravenous urography disclosed a bladder tumour: biopsy specimens showed poorly differentiated keratinising squamous-cell carcinoma with extensive haemorrhage and necrosis. A short course of deep x-ray treatment was followed by total cystectomy and transplantation of ureters into an ileal conduit. Kidney function remained normal with no evidence of recurrence of the systemic lupus erythematosus.

Case 2—A 45-year-old woman presented in 1969 with a five-year history of respiratory symptoms, bilateral pleural effusions, and moderate proteinuria and lupus erythematosus cells on testing. She was three months pregnant. Renal biopsy specimen's showed proliferative glomerulonephritis. She underwent hysterotomy and tubal ligation. Prednisone 50 mg and cyclophosphamide 100 mg daily were started: both were reduced to maintenance dosage but when they were stopped joint swelling recurred.

In 1976, while taking 20 mg cyclophosphamide and 7.5 mg prednisone, she developed left loin pain. Intravenous urography showed a dilated left ureter and calices due to obstruction by bladder tumour. Investigations showed poorly differentiated transitional-cell carcinoma infiltrating muscle. She underwent deep x-ray treatment, total cystectomy, and transplantation of ureters into an ileal conduit. Renal function was normal. Four years after this operation she developed an exacerbation of systemic lupus erythematosus after exposure to sunlight. She responded satisfactorily to steroids alone.

Comment

Carcinoma of the bladder is uncommon in women aged under 40, and invasive carcinoma as found in these two patients is exceptional. Neither had been exposed to any known carcinogen other than cyclophosphamide, but both had received extensive treatment with this drug.

Since the early 1970s evidence has accumulated concerning the carcinogenic properties of cyclophosphamide.¹⁻⁴ Accepting this association, two questions must be answered: Is it justifiable to use the drug? What follow-up should patients receive who have already received the drug? Donadia *et al.*⁵ found no convincing evidence that

cyclophosphamide had any beneficial effect in the treatment of lupus nephritis. It would seem unjustifiable, therefore, to continue its use in this condition.

In other autoimmune conditions and malignant disease we suggest carefully controlled trials of cyclophosphamide, assessing its benefits in each condition, and taking into account the long-term risks before it is accepted as standard treatment. Follow-up of patients who have already received the drug should be of long duration.

Symptoms of cystitis—frequency and dysuria, with or without haematuria or bacteriuria—should be taken seriously, as they are common presenting features of carcinoma of the bladder and assume even more importance in patients who have received cyclophosphamide. A skeleton regimen with individual variations would include six-monthly visits with urological history, urine microscopy, culture, and cytology. If there is a positive response intravenous urography should be performed and, when indicated, cystoscopy. The patient should be advised not to await the next six-monthly appointment if symptoms develop but to report at the earliest opportunity.

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Smoking habits and inflammatory bowel disease: effect on nutrition

Patients with Crohn's disease or ulcerative colitis may become severely wasted during an acute attack of the disease, but chronic under-nourishment is probably more common in Crohn's disease than ulcerative colitis.¹ Although body weight is a useful index of nutritional state, additional information about adipose tissue stores and skeletal muscle mass may be obtained from simple anthropometric measurements.² Patients who give up smoking put on weight, while non-smokers tend to weigh more than smokers.³ We recently found that patients with ulcerative colitis tend to be non-smokers,⁴ and we subsequently investigated the effect of smoking habits on weight and other anthropometric variables in patients with inflammatory bowel disease.

Patients, methods, and results

A total of 106 patients with Crohn's disease (mean age 41 years) and 106 patients with ulcerative colitis (mean age 46 years) who were unselected and attending a gastrointestinal clinic were studied; diagnoses were based on conventional criteria. A control group comprised 106 healthy subjects, mainly hospital employees, matched for age and sex with the patients with Crohn's disease. In all subjects anthropometric measurements were made of height, weight, mid-arm circumference (MAC), triceps skinfold thickness (TSF), and total skinfold thickness at four sites (triceps, biceps, subscapular, and suprailiac). Mid-arm muscle circumference (MAMC) was calculated from the formula $MAMC = MAC - 0.314 \text{ TSF}$.² Observed measurements were expressed as a percentage of ideal standards with the exception of total skinfold thickness, which was expressed in mm. Current smoking habits were documented in all subjects and clinical features of the disease in patients with inflammatory bowel disease.

Non-smokers in the control group and the group with ulcerative colitis were heavier than cigarette smokers and had more subcutaneous fat as

determined by skinfold thickness (significant for triceps skinfold thickness in controls ($p < 0.05$) (table). The difference in measurements between smokers and non-smokers, however, was not evident in the patients with Crohn's disease, except that total skinfold thickness was significantly increased in cigarette smokers compared with non-smokers ($p < 0.05$). Non-smokers with Crohn's disease had significantly lower values for all measurements than non-smokers in the control group and group with ulcerative colitis; these last two groups showed no difference in measurement. Although most of the measurements in cigarette smokers with Crohn's disease were lower than those in cigarette smokers in the control group and the group with colitis, none of the differences achieved significance.

Mean $\pm$ SD anthropometric measurements in non-smokers and cigarette smokers with Crohn's disease and ulcerative colitis, and in controls

	Crohn's disease	Controls	Ulcerative colitis
<i>Non-smokers</i>			
No of patients	55	68	99
Weight (% ideal)	101.7 $\pm$ 18.8**	112.8 $\pm$ 15.8	116.1 $\pm$ 18.6
Mid-arm circumference (% ideal)	93.2 $\pm$ 12.7*	98.7 $\pm$ 9.5	100.9 $\pm$ 11.7
Triceps skinfold thickness (% ideal)	95.4 $\pm$ 43.6*	123.0 $\pm$ 31.6	116.2 $\pm$ 41.4
Total skinfold thickness (mm)	36.8 $\pm$ 28.4**	64.7 $\pm$ 20.1	60.4 $\pm$ 24.9
<i>Cigarette smokers</i>			
No of patients	51	38	7
Weight (% ideal)	102.8 $\pm$ 14.7	108.9 $\pm$ 17.8	103.6 $\pm$ 9.7
Mid-arm circumference (% ideal)	95.0 $\pm$ 12.1	98.6 $\pm$ 10.8	99.3 $\pm$ 6.3
Triceps skinfold thickness (% ideal)	96.4 $\pm$ 35.0	106.3 $\pm$ 38.3	91.3 $\pm$ 31.3
Total skinfold thickness (mm)	49.5 $\pm$ 22.8	56.9 $\pm$ 22.4	58.6 $\pm$ 23.0

* $p < 0.01$ ** $p < 0.001$.

Cigarette smokers in all three groups smoked on average 15-20 cigarettes a day. Duration of disease, activity of disease, steroid treatment, distribution of disease, and extent of resection were similar in both smokers and non-smokers with Crohn's disease.

Comment

Non-smokers with Crohn's disease had significantly reduced weight, muscle bulk, and adipose tissue compared with non-smokers in the control group and the group with ulcerative colitis. The significance, however, disappeared when cigarette smokers in the three groups were compared, though little reliance can be placed on the small group of smokers with ulcerative colitis. Although non-smokers in the control group and the group with ulcerative colitis followed the recognised pattern of being heavier and fatter than cigarette smokers, this was not found in the patients with Crohn's disease. The reason for this apparent discrepancy is not obvious. Both smokers and non-smokers with Crohn's disease were well matched in terms of disease activity, disease distribution, steroid treatment, and previous surgical resection. Anorexia and impaired food consumption are important factors in producing nutritional depletion in active Crohn's disease.¹ Most reports agree that smoking reduces hunger,⁵ and one explanation of our findings may be that patients who already have anorexia due to active disease are relatively unaffected by the additional influence of smoking.

The results emphasise that patients with Crohn's disease are under-nourished compared with a healthy population, and conversely that patients with ulcerative colitis are well nourished. They also highlight the importance of smoking habits in any nutritional study.

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