units and was too large and consistent to be explained by preventive surgery such as coronary artery bypass grafts. A critical examination of the time trends in the use of beta-blocking drugs for the treatment of angina or hypertension might be worth while. The disproportionate decline in the death rates in the youngest age groups in both men and women might be related to either better access to or a greater benefit from medical care. This might apply not only to the management of acute myocardial infarction but to treatment and counselling after infarction (that is, use of beta-blockers and advice on smoking). A change in the natural history of ischaemic heart disease such that it became a "milder" disease might provide an explanation, but why this happened so much later in the United Kingdom than in the USA and Australia would need to be established. A more detailed examination of the changes in lifestyle and medical practice was beyond the scope of this report.

A decline in the rate of death from ischaemic heart disease is thus now apparent; it has many consistencies with changes in fat intake but fewer with changes in smoking habits that have occurred in the UK. If this is the start of a continuing decline in the rate of death from this disease in this country a case may be made for detailed examination of changes in lifestyle and medical practice on a prospective basis to try to find the explanation.

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Neurological effects of recombinant human interferon

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Abstract

Ten women with advanced locally recurrent breast cancer who had failed to respond to radiation and hormonal and cytotoxic agents were given up to 12 weeks of recombinant leucocyte interferon 20×10^6 U/m^2 daily or 50×10^6 U/m^2 three times a week. Within one hour of administration influenza-like symptoms began, which one week later were superseded by lethargy, anorexia, and nausea, with a consequent loss of weight in most patients. Other side effects included profound somnolence, confusion, paraesthesia, and (in one patient) signs of an upper motor neurone lesion in the legs. All these effects together with increased slow wave activity in electroencephalograms from all patients during treatment disappeared when interferon was withdrawn and did not recur on reintroducing the drug at a lower dosage.

Studies are continuing to determine the mechanisms of these effects.

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Introduction

We are conducting a clinical trial to study the efficacy and safety of highly purified human leucocyte A interferon produced by recombinant DNA technology[1] in patients with advanced breast cancer. We report here a previously undescribed complication of interferon—namely, dose dependent, reversible central nervous system toxicity.

Patients and results

All the patients studied had advanced locally recurrent breast cancer which had failed to respond to conventional radiation and hormonal and cytotoxic treatment. Recombinant leucocyte interferon (Hoffmann La Roche) was administered intramuscularly in a dose of either 20×10^6 U/m^2 daily or 50×10^6 U/m^2 three times a week, both regimens being continued for up to 12 weeks. At the time of this report 10 patients had been studied (table).

After initiation of interferon treatment a predictable pattern of side effects common to all patients occurred. Within one hour of injection fever of up to 40°C was noted, which could be subsequently successfully prevented with paracetamol 1 g four times a day. Paracetamol was also effective for headache and myalgia, which were also common during the first four days of treatment. No patients developed any immediate anaphylactic reactions, nor was there any change in blood pressure or other vital signs after injection of interferon. Tachyphylaxis against the influenza-like symptoms rapidly developed over the first week, but at one week these side effects were superseded by lethargy and anorexia. Anorexia was often accompanied by nausea but only occasionally by vomiting; it was enough to cause four patients to refuse food altogether for periods of up to one week, with a subsequent fall in weight of greater than 10% of original body weight. A transient fall in the total white cell and platelet counts was observed but in no patient was this severe enough to warrant withdrawal of treatment. Renal function remained unaltered. Liver function tests showed

Details of patients studied

	Case No									
	1	2	3	4	5	6	7	8	9	10
Age (years)	60	58	61	69	42	58	69	62	63	63
Menopausal state	Post	Post	Post	Post	Peri	Post	Post	Post	Post	Post
Previous treatment:										
Surgery	Mastectomy	Mastectomy	Mastectomy		Mastectomy	Mastectomy	Lumpectomy	Mastectomy	Mastectomy	
Radiation	Chest wall lymph nodes	Chest wall lymph nodes	Chest wall lymph nodes		Chest wall lymph nodes	Chest wall lymph nodes	Chest wall lymph nodes	Chest wall lymph nodes	Chest wall lymph nodes	Chest wall lymph nodes
Hormone	Tamoxifen, norethisterone	Tamoxifen	Tamoxifen, stilboestrol	Tamoxifen	Tamoxifen	Tamoxifen	Tamoxifen	Tamoxifen, norethisterone	Tamoxifen, aminoglutethimide	Methyltestosterone, aminoglutethimide
Chemotherapy			Cyclophosphamide		Vincristine, methotrexate, cyclophosphamide, doxorubicin	Vincristine, cyclophosphamide, 5-fluorouracil, methotrexate		Cyclophosphamide, vincristine, methotrexate, doxorubicin, 5-fluorouracil	Vincristine, doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil	Cyclophosphamide
Oestrogen receptor state	Positive	Negative	Positive	Positive	Negative	Negative	Negative	Negative	Negative	Negative
Site of disease	Chest wall	Axillary nodes	Axilla, chest wall	Bilateral breast	Chest wall	Chest wall	Skin of breast	Chest wall	Chest wall	Chest wall
Dose administered ($\times 10^6$ U)	36-3 daily	36-18, daily	36-18-3, daily	86-45-86, 3 × weekly	36, daily	36-18-9, daily	36-18-3, daily	86-45-9-18, 3 × weekly	86, 3 × weekly	36, daily
Dose limiting side effect	Central nervous system toxicity	Lethargy	Central nervous system toxicity	Lethargy	None	Lethargy	Central nervous system toxicity	Lethargy	None	None
Tumour response*	LPR	NR	LPR	PR	NR	NR	NR	PR	NR	LPR
Outcome	Died after 7 weeks of treatment	Withdrawn at 6 weeks	Treatment interrupted for 7 weeks	Continued with treatment	Died after 2 weeks of treatment	Withdrawn at 8 weeks	Withdrawn at 12 weeks	Continued with treatment	Died after 3 weeks of treatment	Continued with treatment

*LPR = Less than partial response. NR = No response. PR = Partial response (50% reduction).

temporary rises in serum alanine aminotransferase activity without any alteration in the bilirubin concentration.

At the doses given six of the 10 patients developed profound lethargy and somnolence by the third week of treatment, causing them to spend up to 20 hours a day asleep and consequently to refuse to take any form of nourishment. This resulted in appreciable weight loss. Five patients developed frank confusion, loss of concentration, and expressive dysphasia. Two patients developed peripheral paraesthesia and one developed signs of an upper motor neurone lesion in the legs. All patients returned to normal within seven to 10 days of withdrawal of interferon and subsequently tolerated the reintroduction of interferon at a reduced dose.

Investigation of the first patient to develop these effects showed no evidence of intracranial metastases to account for the symptoms. An electroencephalogram taken during the confusional state showed a grossly abnormal pattern with excess of slow wave activity. No baseline tracing had been taken in this patient for comparison. Baseline electroencephalograms were obtained in all subsequent patients admitted to the study, and without exception these were normal. Subsequent electroencephalograms were obtained at four, 12, and 14 weeks. All patients showed abnormal tracings by four weeks of treatment with a diffuse increase in slow wave activity while receiving interferon (figure). One patient developed electrophysiological features in keeping with an early encephalopathy. Repeat electroencephalograms after withdrawal of treatment showed return to normal activity. No patient was found to have intracerebral metastases, which may cause a similar syndrome. Two patients showed regression of observable tumour to more than half its pretreatment size (table).

Electroencephalogram showing diffuse increase in slow wave activity during treatment with interferon.

Discussion

The clinical findings of reversible central nervous system toxicity with high dose interferon are of considerable interest. In our study they were the major cause of dose limiting toxicity. The preparation used was highly purified, and therefore contaminating molecules were unlikely to be the cause. Previous studies have shown that interferon does not cross the blood-brain barrier and cannot be identified in cerebrospinal fluid, even in the presence of high circulating blood concentrations.[2] The mechanism for these effects cannot be explained, and a study is in progress to determine if any subgroups of patients who are at particular risk of developing this distressing syndrome can be identified. It is as yet too early to assess the effectiveness of this interferon in the management of breast cancer.

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Quinine-induced granulomatous hepatitis

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Abstract

Many adverse reactions to quinine have been reported. A 65 year old woman taking quinine sulphate for nocturnal leg cramps presented for investigation of episodes of malaise, fever, nausea, vomiting, and polyarthralgia. Granulomatous hepatitis was diagnosed, for which no common cause was found. She was challenged with quinine sulphate; within hours her temperature had risen and her symptoms returned; transaminase activities rose within 48 hours, as did erythrocyte sedimentation rate. After withdrawal of the drug symptoms abated and transaminase activities returned to normal.

The biochemical response to challenge with quinine implicates the drug as the cause of the liver disturbances. Quinine should be added to the list of drugs known to cause granulomatous hepatitis and should be considered in cases where symptoms are episodic or where no other cause is apparent.

Introduction

Quinine and quinidine are optical isomers, and many adverse reactions, including cinchonism and gastrointestinal and haematological disturbances, are common to both. Quinidine has been reported to induce granulomatous hepatitis.[1] We present the first case report of quinine-induced granulomatous hepatitis.

Case report

A 65 year old woman was referred for assessment of four episodes of malaise, fever, nausea, vomiting, and polyarthralgia over the preceding five months. The episodes were of varying severity and duration, spontaneously subsiding after three to 28 days. There was no known contact with infectious disease and no weight loss. She had been taking pindolol and methyclothiazide daily for two years for hypertension, and quinine sulphate, initially prescribed five months before referral, for noctural leg cramps. Apart from a period in hospital 25 years earlier after a severe reaction to penicillin, she had no medical history of note. She rarely consumed alcohol.

On examination she was obese with a blood pressure of 155/65 mm Hg. She had widespread psoriasis, but no other physical abnormality. Full blood tests showed no abnormality; erythrocyte sedimentation rate was 58 mm in the first hour. Liver function tests showed a bilirubin concentration of 9 μmol/l (0·52 mg/100 ml) (normal 0-29 μmol/l (0-1·7 mg/100 ml)), alkaline phosphatase activity of 306 IU/l (normal 21-266), aspartate transaminase 129 IU/l (normal 10-30), alanine transaminase 298 IU/l (normal 6-36), and γ-glutamyltranspeptidase 238 IU/l (normal 8-63). Serological tests detected no hepatitis B. Other investigations also gave negative results, apart from a positive Mantoux reaction. There was no evidence of active tuberculosis. During the period of investigation the patient felt well, and a spontaneous improvement in the results of liver function tests was noted (fig 1). Percutaneous needle biopsy of the liver showed normal

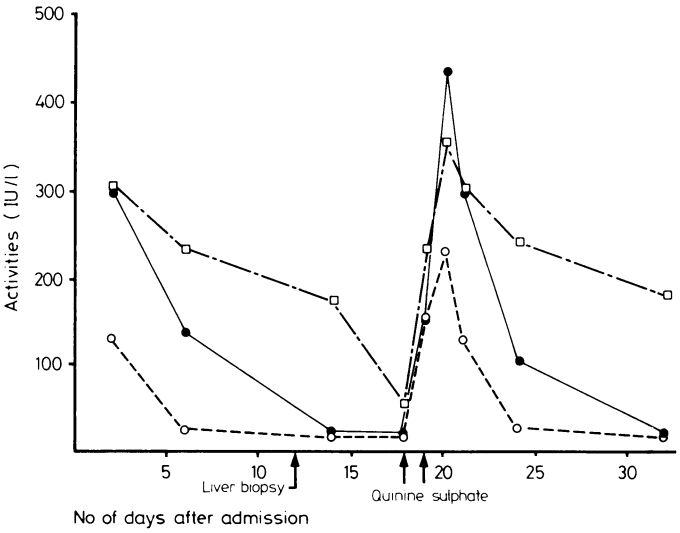

FIG 1—Results of liver function tests showing a transient rise after challenge with quinine sulphate. Normal values: aspartate transaminase (○— — —○) 10-30 IU/l, alanine transaminase (●———●) 6-36 IU/l, alkaline phosphatase (□— - —□) 21-266 IU/l.

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