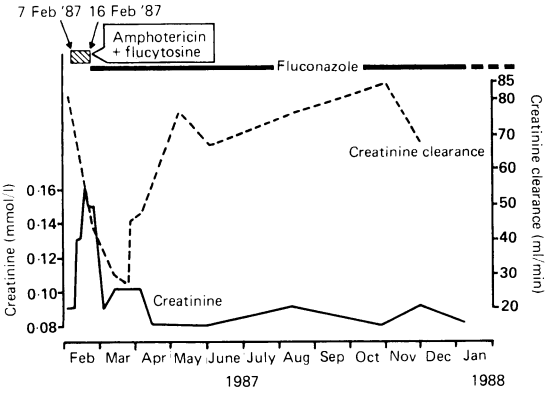

Indicators of renal function during management of relapsed episode of prosthetic valve endocarditis

samples cultured at intervals over the next year grew no pathogens.

Comment

Reviews of candidal endocarditis have noted the high mortality from the condition.[1,2] Survival without surgical intervention is almost unknown and most authorities recommend early replacement of the infected prosthesis. The mainstay of antifungal treatment is amphotericin B, which penetrates poorly into fungal vegetations.[3] Prolonged use of this nephrotoxic drug compounds the problems of possible glomerulonephritis and the use of potent diuretics.

The decision to use fluconazole was based on available evidence that, though the drug is fungistatic and appears to offer no advantage over some other oral agents containing azole in vitro,[4] it is reportedly more active than ketoconazole in vivo.[5] Treatment of the infection in our patient was complicated by cerebral haemorrhage. As there was no evidence of a mycotic aneurysm the cerebral haemorrhage may have resulted from interaction between the anticoagulant and fluconazole, as nicoumalone is metabolised by cytochrome *P*-450 enzymes, which may be inhibited by fluconazole.

The duration of fluconazole treatment was a matter of conjecture. We did not think that serological studies would help in that respect and, though there was no evidence of drug toxicity and renal and liver function values remained normal, we thought it prudent to continue with a maintenance dose for at least the foreseeable future and possibly for life.

We thank Dr C L Bray and Mr R A M Lawson for permission to report this case.

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Thromboses and thromboemboli in patients with lymphoma during cytotoxic chemotherapy

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Deep venous thromboses cause appreciable morbidity and are potentially fatal. Sixty per cent of deaths due to pulmonary emboli occur in patients in whom such a diagnosis was not suspected.[1] Most patients will survive if treated with anticoagulant drugs, and the long term prognosis is good, with an overall rate of recurrence of emboli of about 10%, which is lower if a reversible precipitating cause is present.[1]

We report on two patients with pulmonary emboli and three others with deep venous thromboses that developed during cytotoxic chemotherapy for malignant lymphomas.

Patients, methods, and results

We examined the records of 49 consecutive patients in whom malignant lymphoma had been recently diagnosed. Five patients with stage 1 non-Hodgkin's lymphoma were treated by radiotherapy alone. Combination chemotherapies for 12 patients with Hodgkin's lymphoma and six with non-Hodgkin's lymphoma were vinblastine 6 mg/m^2 intravenously on days 1 and 8 and procarbazine 150 mg, chlorambucil 6 mg/m^2, and prednisolone 40 mg all given orally each day for 14 days. Cycles were repeated every 28 days. In a subgroup of patients this combination of chemotherapy was alternated with doxorubicin 25 mg/m^2, bleomycin 10 mg/m^2, dacarbazine 375 mg/m^2, and vincristine 2 mg given intravenously on days 1 and 15. Seventeen patients with high grade non-Hodgkin's lymphoma were given cyclophosphamide 750 mg/m^2, doxorubicin 40 mg/m^2, vincristine 2 mg, and bleomycin 10 mg intravenously on day 1; prednisolone 40 mg orally on days 1-5; and methotrexate 200 mg/m^2 intravenously on day 15 with folinic acid on day 16. Cycles were repeated every 21 days. Nine patients with intermediate or low grade non-Hodgkin's lymphoma were given chlorambucil 10 mg and prednisolone 40 mg orally each day for 10 days with vincristine 2 mg intravenously on day 1. Cycles were repeated every 21 days.

The five patients who developed thromboses or thromboemboli did so after starting combination chemotherapy, to which they all responded. The table shows their clinical details. The thromboses and thromboemboli developed quickly (median 4 weeks, range 2-15 weeks) and resolved rapidly with intra-

Characteristics of patients with deep venous thromboses or pulmonary emboli

Case No	Age (years)	Sex	Lymphoma type	Vascular events	Site of lymphoma	Chemotherapy
1	59	M	Non-Hodgkin's	Multiple pulmonary emboli	Mediastinum	Chlorambucil, prednisolone, vincristine
2	54	F	Non-Hodgkin's	Multiple pulmonary emboli	Lung, peri-renal	Vinblastine, procarbazine, chlorambucil, prednisolone
3	52	M	Non-Hodgkin's	Leg deep vein thrombosis	Mediastinum	Cyclophosphamide, doxorubicin, vincristine, bleomycin, prednisolone, methotrexate, folinic acid
4	38	F	Hodgkin's	Axillary vein thrombosis	Mediastinum, spleen, liver	Vinblastine, procarbazine, chlorambucil, prednisolone
5	26	F	Hodgkin's	Axillary vein thrombosis	Lung	Vinblastine, procarbazine, chlorambucil, prednisolone

venous heparin and warfarin, which was given orally for about six months. One patient (case 1) required radiotherapy for a recurrence of a localised lymphoma but thereafter remained free of a recurrence 30 months after starting chemotherapy. Three patients showed no recurrence of lymphoma 14, 18, and 21 months after starting chemotherapy, and the last patient (case 5) was in remission, having recently completed chemotherapy.

Comment

Patients with cancer have an increased risk of thromboses.[2] The mechanisms are obscure but tumours may release unknown substance(s) into the circulation that directly or indirectly activate the coagulation system. This risk may be enhanced by cytotoxic chemotherapy as shown in patients with breast cancer.[3] Of a series of 117 patients with Hodgkin's lymphoma, 10 developed venous thromboses, mostly during cytotoxic chemotherapy,[4] as did our five patients, suggesting a causal role for chemotherapy. Support for vascular toxicity induced by chemotherapy was suggested by an in vitro model, which showed endothelial damage by a variety of cytotoxic drugs.[5] Alternatively, the presence of masses from lymphomas in the lungs or mediastinum could impair venous return and induce stasis, thereby enhancing an underlying predisposition to thromboses.

Despite the uncertainty about the cause of thromboses and thromboemboli in our patients their early recognition and treatment can lead to long term survival when the underlying lymphomas are controlled by chemotherapy.

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Fish oil and plasma fibrinogen

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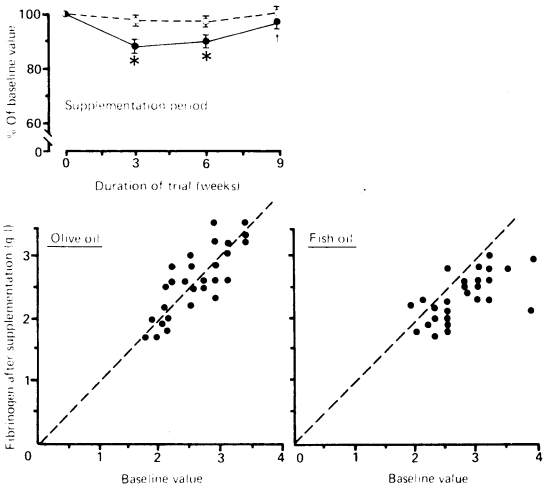
The low morbidity from ischaemic heart disease in people who eat large amounts of fish has been attributed to possible hypolipidaemic and antithrombotic effects of fish oils.[1] Intake of marine oils has been shown to lower plasma triglyceride and cholesterol concentrations, decrease thrombocyte aggregability, and increase the bleeding time.[1] As plasma fibrinogen is essential for the formation of thrombus and the risk of coronary disease is positively correlated with the plasma fibrinogen concentration,[2] we decided to see whether fish oils might possibly affect plasma fibrinogen concentrations.

Case report

Sixty four men aged 35-40 were randomly assigned to two equal groups. In a double blind trial one of the groups was given for six weeks 14 g fish oil concentrate daily (as 1 g capsules) containing 25·7% eicosapentaenoic acid (C20:5, n-3) and 20·5% docosahexaenoic acid (C22:6, n-3; Apothekernes Laboratorium AS, Norway). The other group was given 14 g olive oil daily as 1 g capsules, also for six weeks. Compliance was good, as judged from plasma fatty acid responses. Some men reported belching as a minor problem. There were five dropouts in the fish oil treated group and three in the olive oil treated group. Citrated plasma for measurement of fibrinogen concentrations was obtained before the trial (zero time) and after three, six, and nine weeks. Plasma fibrinogen value (as thrombin coagulation time[1]) was estimated by an automated method.

Mean plasma fibrinogen concentrations in the fish oil and olive oil treated groups at zero were 2·73 and 2·66 g/l. After three weeks in men taking the fish oil concentrate there was a significant decrease (13·2%; $p<0·05$) in plasma fibrinogen concentrations, but no further change was seen three weeks later (figure). Three weeks after stopping fish oil supplementation plasma fibrinogen concentrations had returned almost to initial values. In men taking olive oil capsules there was no significant change in plasma fibrinogen concentrations. To see whether the effect of the fish oil was related to initial plasma fibrinogen concentrations baseline fibrinogen values for each group were plotted against individual mean values—that is, at three and six weeks—after supplementation (figure). By analysis of covariance no such relation could be found.



Upper panel: Change in plasma fibrinogen concentrations in two groups of men taking dietary supplements of fish oil (●) or olive oil (○). (Points are means. Bars are SE.) Lower panels: Individual mean plasma fibrinogen concentrations—that is, at three and six weeks—after supplementation with olive oil and fish oil plotted against baseline values.
**Compared with zero time $p<0·05$ (paired samples t test).*
†Compared with three weeks $p<0·05$

There was a weak but significant positive correlation between smoking and plasma fibrinogen concentration ($r=0·260$; $p<0·01$). No difference in the effect of fish oil on plasma fibrinogen concentration between smokers and non-smokers could, however, be detected.

Comment

To our knowledge this is the first report that the plasma fibrinogen concentration may be reduced by dietary fish oils. Our results raise the question whether the suggested antithrombotic effect of fish oils[1] might be related to a lowering of plasma fibrinogen. The reported lack of a fibrinogen lowering effect of cod liver oil[4] may be related to the lower dose of n-3 fatty acids