estimation of daily excretion of protein in patients who may be unable to provide an accurately timed collection.

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Role of hepatic arterial embolisation in the carcinoid syndrome

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Abstract

Eighteen patients with severe symptoms of the carcinoid syndrome were assessed for hepatic embolisation. Four were too ill, and one had mild symptoms; thus 13 received a periembolisation regimen of cyproheptadine, fenclonine, aprotinin, methylprednisolone, tobramycin, flucloxacillin, and metronidazole. Embolisation was not performed in one patient with an occluded portal vein and was unsatisfactory in two others, in one because she was moribund and in the other because the hepatic artery had been ligated. Dramatic improvement in symptoms occurred in the nine patients in whom embolisation was successfully carried out, with abolition of flushing, severe abdominal pain, and wheeze and reduction in diarrhoea from 10·5 (SD 7·6) to 1·6 (0·9) stools/day. Urinary excretion of 5-hydroxyindole acetic acid fell from 1048 (716) to 289 (184) μmol/24 h (200 (137) to 55 (35) mg/24 h). Complications included one death from septicaemia, a hepatic abscess requiring surgical drainage, abdominal pain in three patients, pleural effusion in two, and transient encephalopathy in one. Relief of symptoms lasted for one to 24 months, and second embolisation in two patients produced further remissions of four to six months. Five patients died, one to 40 months after embolisation, in four cases because of metastases or heart failure.

Hepatic embolisation is the treatment of choice for symptoms of the carcinoid syndrome resistant to medical treatment.

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Introduction

The carcinoid syndrome is characterised by flushing, diarrhoea, heart disease, and wheezing and in most cases is associated with extensive metastases from a malignant gastrointestinal tumour.[1] In general these tumours are of low grade malignancy, and survival of up to 20 years despite symptoms has been reported.[2] Nevertheless, the range of the disease is wide, and other series

have shown a much shorter mean survival time. In one series of patients with carcinoid tumours and proved metastases mean survival was only months.[3] By the time the syndrome is present the tumours have produced extensive metastases, and therefore traditional modes of management include pharmacological modification of the symptoms, limited surgical procedures to reduce tumour bulk or devascularise hepatic metastases, and cytotoxic treatment. Each of these approaches has its limitations and hazards, and all have proved disappointing.[4]

Allison *et al* from this institution reported that in two patients with the carcinoid syndrome and extensive metastases the symptoms initially responded dramatically to hepatic arterial embolisation.[5] We describe our experience with this therapeutic approach over the past six years and give the long term results, benefits, and potential hazards.

Patients and methods

PATIENTS

Eighteen patients (12 men, six women; aged 38-76) with the carcinoid syndrome have been considered for hepatic arterial embolisation in the past six years. All had had symptoms of the syndrome for at least six months, the range being six months to eight years. All 18 patients had noticed episodic or continuous flushing, 13 had had diarrhoea, 13 peripheral oedema, 12 signs of carcinoid heart disease, seven abdominal pain, four wheezing, and five a pellagroid rash.

All patients were admitted for assessment to establish the severity of the symptoms and define the extent of metastatic spread of the tumour. This included clinical assessment of symptoms, use of various imaging techniques to define tumour deposits, and measurement of 24 hour urinary excretion of 5-hydroxyindole acetic acid. One patient suffered only from mild flushing precipitated by drinking alcohol or exercise. She was treated by dietary advice alone and was followed up in the outpatients clinic; her symptoms had not progressed two years later. Four patients were not considered for embolisation because of advanced disease, and indeed three of these died during their first admission to our unit. We therefore selected 13 patients for embolisation in whom symptoms were severe and had become resistant to pharmacological agents.

METHODS

Before the procedure each patient began a regimen designed to prevent complications arising from release of tumour metabolites. Forty eight hours before embolisation cyproheptadine (a serotonin blocker) 4 mg thrice daily by mouth and fenclonine (an inhibitor of synthesis of serotonin) 4 mg thrice daily by mouth were started. A central venous line was inserted. On the day of embolisation the patient was premedicated with papaveretum and scopolamine, and cloxacillin 500 mg four times intravenously or by mouth, tobramycin 80 mg thrice daily intravenously or intramuscularly, and metronidazole 500 mg four times daily intravenously or by mouth were started. Just before the procedure methylprednisolone 1 g was administered and an aprotinin infusion of 50 000 IU/h started. Within the angiographic suite human plasma protein fraction was available in case hypotension occurred and hydralazine (10-15 mg intravenously) for hypertension.

The femoral artery was cannulated under local anaesthesia, the coeliac axis entered, and contrast medium injected. The arterial phase was studied to define the extent of the hepatic metastases, and the venous phase to determine the degree of patency of the portal vein—an essential preliminary step. If the portal vein was patent then the hepatic artery or its branches were selectively catheterised and the tumour vasculature embolised. Initially small pieces (1-3 mm) of slowly absorbed gelatin sponge (Sterispon, Allen and Hanbury's) was used to embolise the vessels, but subsequently a mixture of Sterispon and human dura mata (Lyodura, Davis and Gear) in 25% dextrose, tobramycin, and contrast medium was used, and steel coils were inserted in segmental arteries. A further angiographic study was performed to check that the embolisation was satisfactory.

After embolisation pulse and blood pressure were monitored closely for 24 hours, pethidine was given as required for analgesia, and aprotinin was continued for 48 hours. Fenclonine and cyproheptadine were stopped after four to five days. Initially, we continued antibiotics for five days, but later we continued them for 10 days or for longer if fever persisted.

Results

Twelve of the 13 patients who proceeded to angiography underwent embolisation: in one patient the coeliac axis injection showed an occluded portal vein, which is a contraindication to embolisation. Embolisation was unsatisfactory in two further patients. In one the hepatic artery had been previously ligated, which prevented adequate embolisation, and the other was severely ill (see below).

Early complications of embolisation—One of the 12 patients who underwent embolisation died from a cardiac arrest within a few hours after the procedure. She had been moribund before the procedure with cachexia, heart failure, and massive hepatomegaly. She was one of the early patients in this series, and subsequently embolisation was not performed in such severely ill patients. Another patient who had initially responded to the procedure died eight days later despite an initial amelioration of symptoms. Antibiotics were stopped on day 5, but she then developed septicaemia, from which she died. This death also occurred early in the series, and subsequently antibiotics were continued for longer. One patient responded well to embolisation but had a prolonged fever that continued for three to four weeks. When antibiotics were stopped after that time he developed septicaemia, and a gas filled cavity in the liver was evident on *x* ray examination. At laparotomy a hepatic abscess was drained and a necrotic gall bladder removed. He subsequently recovered and remained symptom free. One patient developed jaundice, encephalopathy, and hypotension three days after embolisation, aprotinin having been stopped. Aprotinin was restarted, and he recovered slowly over the next few days. Other complications were minor. Five patients developed abdominal pain with or without a friction rub, which was treated with pethidine. A right sided pleural effusion occurred in two patients but settled spontaneously. Three patients developed hypertension during or within 12 hours after the procedure but all three responded to hydralazine.

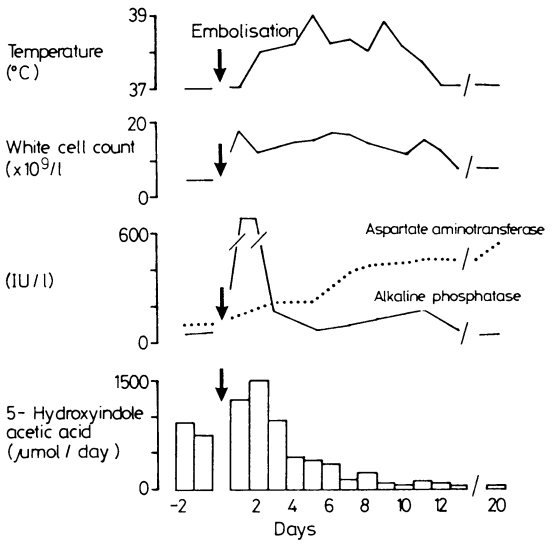

FIG 1—Effect of hepatic embolization on clinical and biochemical variables in patient with carcinoid syndrome.
Conversion: SI to traditional units—5-Hydroxyindole acetic acid: 1 μmol/day ≈ 191 μg/day.

Chemical and laboratory variables of successful embolisation—Figure 1 shows the effects of a typical successful embolisation on several clinical and laboratory variables. After embolisation fever and leucocytosis occurred associated with negative blood cultures, which were presumably due to tissue necrosis. Serum transaminase activities rose acutely after embolisation (in this case to over 2000 IU/l), and alkaline phosphatase activities showed a slow but prolonged rise. Bilirubin concentrations did not change. Excretion of 5-hydroxyindole acetic acid, which was raised before embolisation, rose further, presumably due to release of serotonin and its metabolites from

necrotic tumour, and then fell to below the values found before embolisation. This pattern of response was found in all patients in whom embolisation was successful.

Early effects of embolisation on symptoms and signs—All patients who lived for at least five days after embolisation noted either considerable reduction or complete abolition of their symptoms after embolisation. Flushing was abolished in all eight patients in whom it had been a major symptom, and abdominal pain was relieved in the four patients in whom it had been troublesome. In the two patients with wheeze embolisation produced complete symptom relief. Stool frequency in the five patients who had had diarrhoea before embolisation fell from 10·5 (SD 7·6) stools/day before embolisation to 1·6 (0·9) stools/day after embolisation. This difference is more important than it appears because before embolisation these patients had been taking symptomatic treatment including codeine, loperamide, cholestyramine, and methysergide and after embolisation these medications were reduced or stopped. In keeping with the clinical evidence of improvement urinary secretion of 5-hydroxyindole acetic acid fell from 1048 (716) to 289 (184) μmol/24 h (200 (137) to 55 (35) mg/24 h) (normal 100 μmol/24 h (19·1 mg/24 h)). The liver did not change in size but did seem to become harder after embolisation. Cardiac signs did not change.

Late effects of embolisation—Figure 2 shows the effects of embolisation on the duration of remission of symptoms and subsequent course. Complete remission of symptoms lasted up to 18 months, and when symptoms recurred they were not as severe as before, at least initially.

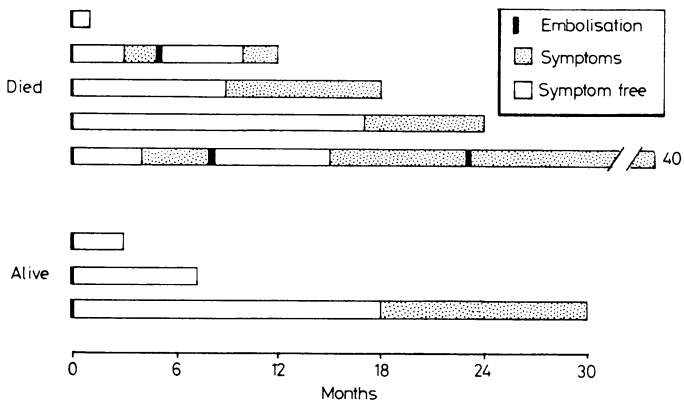

FIG 2—Effect of hepatic embolisation on symptom relief and survival in patients with carcinoid syndrome. Each horizontal bar represents one patient.

Two patients with recurrent symptoms were assessed as being suitable for a second embolisation and had further remissions of symptoms for up to six months. Subsequent embolisation in one of these patients, however, had no beneficial effect. Five of the eight patients died; one, who had been symptom free, died of an unrelated cause one month after embolisation, and the others, all with recurrent symptoms, died of advanced carcinoid disease. All these patients had metastases in sites other than the liver, such as the bones, skin, and lungs, and three had severe heart disease, as well as flushing and diarrhoea. In those patients who died the mean survival after embolisation was 1·6 (1·2) years. Survival time from the first symptom in these patients was 4·2 (3·2) years, compared with 2·9 (1·7) years in patients in whom embolisation was not performed.

Discussion

The main objective of hepatic embolisation was to relieve the severe intractable symptoms of the carcinoid syndrome. In each case flushing, diarrhoea, or hepatic pain had become intolerable despite high doses of blocking agents or analgesics. In all patients who could be adequately assessed the procedure did indeed relieve symptoms, and these remissions lasted for up to 18 months. That this response was due to reduction in tumour mass was evidenced by the variables of cell necrosis at the time of embolisation and the subsequent fall in urinary excretion of 5-hydroxyindole acetic acid and results of liver imaging tests.

Embolisation would seem to offer appreciable advantages over surgery and chemotherapy in advanced cases of the carcinoid syndrome. Surgery in these patients has a high mortality, and anaesthetic problems are considerable.[6] Furthermore, the morbidity associated with any surgery, even hepatic artery ligation,[7] in patients with advanced carcinoma and a limited prognosis is considerable, and ligation as a method of devascularisation does not seem to be effective as an extensive anastomotic circulation rapidly develops.[8] This is not seen with embolisation because the technique occludes the small vessels as well as the large ones, preventing establishment of a collateral supply.[5] Results of cytotoxic treatment in the carcinoid syndrome have been disappointing, whether single or multiple agents have been used.[4 8] Although some reduction in liver size has been documented, symptomatic response has been poor, and indeed symptoms may be exacerbated, presumably because of tumour necrosis.

Certain technical aspects of the embolisation procedure are worth emphasising. To avoid immediate complications of hypotensive or hypertensive crises, hypoglycaemia, encephalopathy, profound flushing, and hyperdynamic circulation it is necessary to block the actions of agents produced by the tumours, as described above. This seems to have been successful in all but one of our patients and contrasts with previous reports of surgery, devascularisation, and cytotoxic treatment.[4 6 7] Furthermore, since the surviving liver depends entirely on the portal venous supply after embolisation it is essential that the patency of the portal vein is established first. The necessity for a prolonged course of broad spectrum antibiotics after embolisation until fever disappears is emphasised by the fact that the major complications of embolisation in this series were due to infection of necrotic liver tissue. Although in one of the cases in this series the presence of gas in the liver was associated with a hepatic abscess, this is not always so. Parenchymal gas may be demonstrated in the embolised liver in one third of all patients in whom embolisation has been performed but is only occasionally associated with infection.[9]

The survival time of patients in this series was not long. All these patients, however, had had severe symptoms for months or years, and many also had carcinoid heart disease or metastases beyond the liver, or both. These factors limit the survival of patients, no matter how successful the hepatic embolisation. It is therefore not clear from our data whether hepatic embolisation increases (or even decreases) life expectancy. In addition, the optimal selection policy for embolisation was not established. Nevertheless, hepatic embolisation improved symptoms and lifestyle, and these improvements ranged from considerable to spectacular. One patient, who had been totally incapacitated by severe flushing and diarrhoea resistant to methysergide and other agents, had 18 months of symptom free life.

We believe that the advantages of embolisation are great despite the problems encountered in this series. The two deaths were avoidable: we no longer perform embolisation in preterminal patients, and we continue antibiotics for longer periods. This current practice should be associated with much lower mortality, and morbidity should be limited to minor complications such as pain or hypertension. As the cystic artery is a branch of the hepatic, however, necrosis of the gall bladder remains a risk of hepatic embolisation.

It is not clear at present which patients will benefit most from embolisation. Patients who are well apart from occasional symptoms may remain fit for some years without any treatment, but possibly embolisation at this stage would prolong life. At present, however, we suggest that patients with severe symptoms of the carcinoid syndrome resistant to pharmacological agents should be assessed for embolisation, and if there are extensive hepatic deposits embolisation rather than surgery or cytotoxic treatment is the treatment of choice.

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Lacunar infarcts in polycythaemia with raised packed cell volumes

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Abstract

Lacunar (small deep cerebral infarcts) infarction is described in association with raised packed cell volumes. Two patients had polycythaemia vera, one stress polycythaemia. They presented with transient ischaemic episodes and were shown by computed tomography to have lacunes deep in the basal ganglia and internal capsule. Such lesions may be caused by small vessel occlusions related to increased viscosity and impaired oxygen consumption by adjacent tissues. Finding a raised packed cell volume in patients with lacunes and transient ischaemic attacks offers a further possibility of treatment.

Introduction

Lacunes are small (0·5-15 mm) infarcts in the basal ganglia, internal capsule, and basis pontis resulting from occlusion of penetrating small arteries.[1 2] They also result from rupture of microaneurysms. Fisher examined 114 brains with lacunes and found an association with hypertension in all but one patient.[2] We describe three patients who had lacunes in association with a raised packed cell volume due to polycythaemia, an association not previously described.

Case reports

Case 1—A 66 year old man had a two year history of sudden attacks of tingling in the left forearm with difficulty in grip for three minutes, averaging six attacks a year. There were no features affecting the face, speech, vision, or leg. Five weeks before admission he lost control of his legs, wobbled and staggered, but recovered in three minutes. He was alert with no plethora; the blood pressure was 130/80 mm Hg in both arms; the heart and chest were normal. The liver was four finger breadths enlarged and the spleen was palpable. No neurological abnormality was detected apart from heel-shin ataxia in the left leg. Investigations showed a normal chest *x* ray film; haematological values are shown in the table. Biochemical profile, liver function tests, and coagulation profile were normal. Diagnostic sonar confirmed enlargement of the liver and spleen. Bone marrow showed marrow particles of increased cellularity; all three cell lines were very active with prominent megakaryocytes, the iron stores being reduced. These appearances were compatible with polycythaemia vera. He was treated with venesection and later with ^{32}P.

Haematological values in the three patients

Values	Case 1	Case 2	Case 3
Haemoglobin (g/dl)	17·6	17·7	18·0
Red cell count ($\times 10^{12}$/l)		6·34	5·90
Packed cell volume	0·55	0·572	0·539
White cell count ($\times 10^{9}$/l)	9·5	13·3	6·9
Platelets ($\times 10^{9}$/l)	883		315
Erythrocyte sedimentation rate (mm in 1st h)	<1	<1	1
Red cell volume (ml/kg)	32		33
Plasma volume (ml/kg)	33		

Case 2—A 66 year old male calligrapher presented with two episodes of transient weakness of his left arm and left leg; he had difficulty formulating written letters, with occasional hesitancy in speech and poor verbal memory. Polycythaemia vera had been diagnosed at another hospital (table), and he had been treated with 4 mCi of ^{32}P. His blood pressure was 170/100 mm Hg, the heart and chest being normal. There were no carotid bruits. His liver was enlarged three finger breadths; the spleen was not felt. He had a left sided homonymous hemianopia, dysgraphia, and nominal dysphasia. Computed tomography showed bilateral lacunes (fig 1).

Case 3—A 49 year old man first presented with sudden dizziness, slurred speech, and clumsiness while walking. His general practitioner found that he had a blood pressure of 210/115 mm Hg and grade II hypertensive retinopathy and treated him with atenolol and hydralazine. A month later he complained of episodic paraesthesiae in the left arm, face, and leg with slurred speech. He smoked 15 cigarettes a day. At hospital he was found to be plethoric with a blood pressure of 150/100 mm Hg. His heart, chest, and abdomen were all normal. The peripheral pulses were normal with no bruits in the neck. Fundi showed grade II hypertensive retinopathy. There was minimal ataxia of fine movement of the left hand, but no other abnormal signs. Haematological values are shown in the table. Stress polycythaemia was diagnosed, and computed tomography showed a lacune in the right thalamus (fig 2). He was treated by repeated venesection.

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