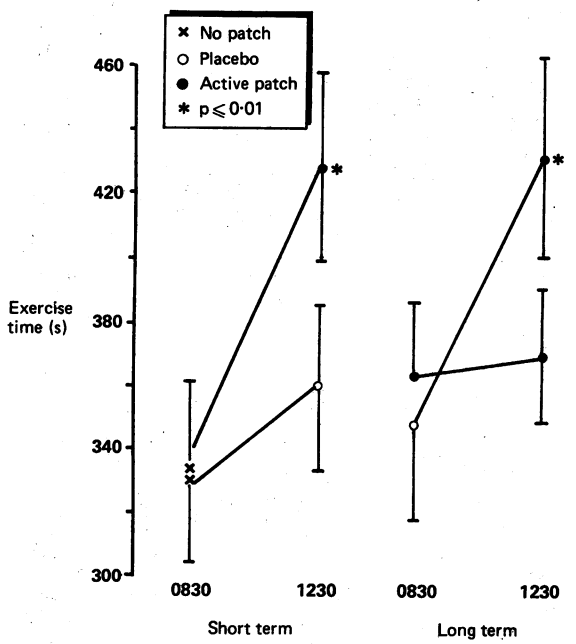
Patients had a history of classical, stable, exertional angina; a previous positive exercise test; and proved responsiveness to nitrates (exercise time prolonged by at least one minute after sublingual glyceryl trinitrate). No patient had previously taken long acting nitrates, and no nitrates other than sublingual glyceryl trinitrate were taken during the study.

In the study of short term efficacy the active patch prolonged exercise time by 68 seconds compared with the placebo (95% confidence interval 24 to 111 seconds, $p<0.01$) (figure). In the long term phase (0830 tests) there was no significant difference in exercise time during continuous active treatment compared with the placebo period of intermittent treatment. By contrast, during the active period of intermittent treatment (1230 tests) exercise time was prolonged by 62 seconds (confidence interval 18 to 105 seconds, $p=0.01$) compared with continuous treatment.



Mean (SEM) results of exercise testing in short term and long term studies of glyceryl trinitrate treatment. In the short term phase patients underwent exercise testing at 0830, received a patch at 0900, and were retested at 1230. In the long term phase patients underwent exercise testing at 0830 with the previous evening's patch in position (comparison between continuous active treatment and placebo period of intermittent treatment); received an active patch at 0900; and were retested at 1230 (comparison between continuous active treatment and active period of intermittent treatment).

In the short term phase ST depression at maximum common exercise time was significantly reduced after application of an active patch compared with placebo (difference=0·36 mm, confidence interval 0·16 to 0·55 mm, $p<0.01$). In the long term phase no difference was observed between continuous active treatment and the placebo period of intermittent treatment. By contrast, during the active period of intermittent treatment a reduction in ST depression still occurred (difference 0·37 mm compared with continuous treatment; confidence interval 0·07 to 0·68 mm, $p<0.05$). At peak exercise there was no significant effect on ST depression in either phase.

There was no evidence of exacerbation of anginal symptoms during overnight placebo treatment in the intermittent phase (1·0 (SEM 0·5) episode/patient week with intermittent treatment; 1·0 (0·5) with continuous treatment).

Comment

Our results support previous studies which showed that a high degree of tolerance develops during continuous use of glyceryl trinitrate patches.[4,5] The prolonged exercise time and reduced ST depression at maximum common workload that occurred with short term administration were virtually abolished after one week of continuous treatment. By contrast, tolerance did not occur during intermittent treatment and beneficial effects were maintained.

There was no evidence of exacerbation of anginal symptoms overnight, when no nitrate was being supplied. Nevertheless, we are wary of extending our conclusions to all patients with angina, particularly those with angina decubitus.

The problem of nitrate tolerance is not confined to patch treatment, and the implication for all nitrate preparations is that dosage regimens should be tailored to each patient to provide protection at times of maximum susceptibility. Attempted 24 hour protection may be self defeating.

1 Rudolph W, Blasini R, Reiniger G, Brugmann U. Tolerance development during isosorbide dinitrate treatment: can it be circumvented? *Z Kardiol* 1983;72(suppl 3):195-8.
2 Silber S, Krause KH, Garner C, Theisen K, Jahrmarker H. Anti-ischaemic effects of an 80 mg tablet of isosorbide dinitrate in sustained release form before and after 2 weeks' treatment with 80 mg once daily or twice daily. *Z Kardiol* 1983;72(suppl 3):211-7.
3 Parker JO, Vankoughnett KA, Farell B. Comparison of buccal nitroglycerin and oral isosorbide dinitrate for nitrate tolerance in stable angina pectoris. *Am J Cardiol* 1985;56:724-8.
4 Cowan JC. Nitrate tolerance. *Int J Cardiol* 1986;12:1-19.
5 Charash B, Scheidt SS. The controversy over transdermal nitroglycerin: an update. *Am Heart J* 1986;112:207-15.

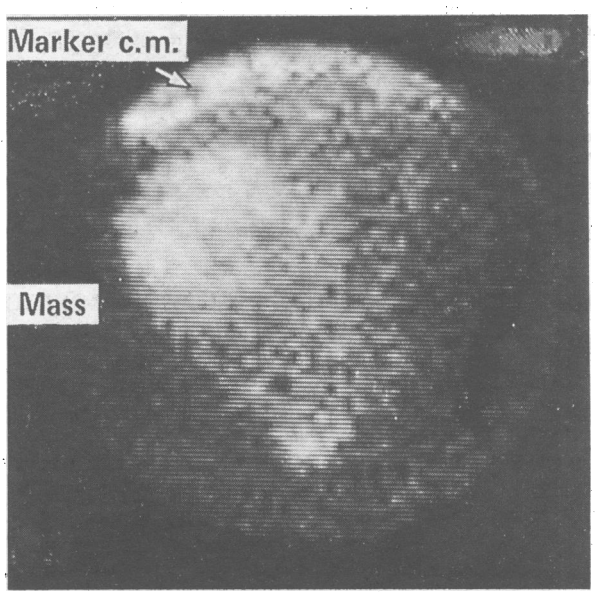
(Accepted 21 October 1986)

Department of Cardiology, University of Newcastle upon Tyne, Freeman Hospital, Newcastle upon Tyne NE7 7DN
CAMPBELL COWAN, DPHIL, MRCP, honorary senior registrar and Squibb cardiovascular research fellow
JOHN BOURKE, MRCPI, honorary senior registrar
DOUGLAS S REID, FRCP, consultant cardiologist
DESMOND G JULIAN, MD, FRCP, professor of cardiology

Correspondence to: Dr Cowan.

Immunoscintigraphy of metastases with radiolabelled human antibodies

A lymphoblastoid cell line, secreting human immunoglobulin, has been produced by transformation of lymph node lymphocytes, recovered at operation for pancreatic adenocarcinoma, using Epstein-Barr virus.[1] Specific antibody secreting clones were selected by testing the supernatants from the lymphoblastoid cells against the same tumour cells and other cell lines, using a modified enzyme linked immunosorbent assay (ELISA) with the cells adherent to microtitre plate wells.[2] In addition, antibody specificity was confirmed by lack of binding to various cell lines: with *o*-phenyldiamine as substrate the mean value of five spectrophotometric determinations of binding of the human antibody to the pancreatic adenocarcinoma cells was 0·973 (SD 0·129) compared with 0·153 (0·088) for all other cell lines assessed.[3] The antibody was shown to be of the IgG class and was labelled with iodine-131 by the "iodogen" method.[4] We used this human antibody to assess the extent of a growth in a patient with secondary disease.



Radioimmunoscintigram: anterior view of abdomen at 20 hours. A focal area of increased uptake is seen just below the liver area (mass). A marker was placed over the costal margin (c.m.).

Case report

A 54 year old woman had undergone a Whipple's operation 10 months previously for a pancreatic adenocarcinoma, which had been histologically classified as a poorly differentiated carcinoma. After clinical diagnosis of hepatic secondaries she was admitted to the surgical unit for further investigations. Ultrasonography showed the presence of a large solid tumour associated with the

inferior surface of the liver; technetium-99m scanning, unexpectedly, did not identify this mass clearly within the liver area, although it showed a suspicious area at the lower edge of the liver.

We decided to use the human antibody as a possible targeting agent to delineate the extent of secondary growth. Thyroid uptake was blocked by 60 mg potassium iodide twice daily for two days before the procedure and thereafter for four days. A test dose of 50 μg unlabelled antibody (sterilised by a 0·22 μm filter) was administered intradermally and confirmed the absence of hypersensitivity. The patient's informed consent and the approval of the hospital ethical committee were obtained.

A total dose of 700 μg antibody labelled with 1·5 mCi ^{131}I was injected intravenously. Immunoscintigraphy showed that within 45 minutes the radioactivity had concentrated in the liver area. At four hours this area was judged to be clear of iodine but some iodine was present in the right kidney and the bladder. After 20 hours the radioactivity coincided with the area corresponding to the subhepatic mass seen on ultrasonography (figure); the ^{131}I in this area persisted for 24 hours.

Comment

There have been several attempts at immunoscintigraphy with rodent monoclonal antibodies labelled with various radioactive ligands.[4] Epstein-Barr virus transformation of committed lymphocytes offers great potential in the production of antitumour antibodies of human origin. The degree of specificity in this case was remarkable and the dose given far below that normally used with mouse antibodies. A major problem with this type of viral transformation, however, is the low amounts of antibody secreted. Back fusion of these antibody secreting lymphoblastoid lines with other cell lines can increase this secretion and stabilise the hybrid lines produced.[5]

We thank the medical physics department, Stobhill Hospital, and the department of radiotherapy, Western Infirmary, Glasgow. We also thank Dr D Sumner, Stobhill Hospital, for his invaluable help in interpreting the data.

1 Steinitz M, Klein G, Koskimies S, Makela O. EB virus induced lymphocyte cell lines producing specific antibody. *Nature* 1977;**269**:420-2.
2 Stimson WH, Al-Azzawi F, McAdam A. Monoclonal antibodies to human pregnancy serum-derived immune complexes react with ovarian cancer antigens. *Biochemn Soc Trans* 1985;**13**: 369-70.
3 Stimson WH, McAdam A, Lang G, Dodd J. Pregnancy-associated β_1-macroglobulin: detection on the surface of ovarian cancer cell lines. *Int J Cancer* 1985;**35**:185-7.
4 Epenetos AA, Britton KE, Mather S, *et al.* Targeting of iodine-123-labelled tumour-associated monoclonal antibodies to ovarian, breast and gastro-intestinal tumours. *Lancet* 1982;ii:999-1004.
5 Kozbor D, Lagarde AE, Roder JC. Human hybridomas constructed antigen-specific Epstein-Barr virus-transformed cell lines. *Proc Natl Acad Sci USA* 1982;**79**:6651-5.

(Accepted 15 October 1986)

Immunology Division, Strathclyde University, and Department of Surgery, Stobhill Hospital, Glasgow
F AL-AZZAWI, MRCOG, research fellow
J SMITH, FRCS, consultant surgeon
W H STIMSON, PHD, professor of immunology

Correspondence to: Dr F Al-Azzawi, Department of Obstetrics and Gynaecology, University of Cambridge.

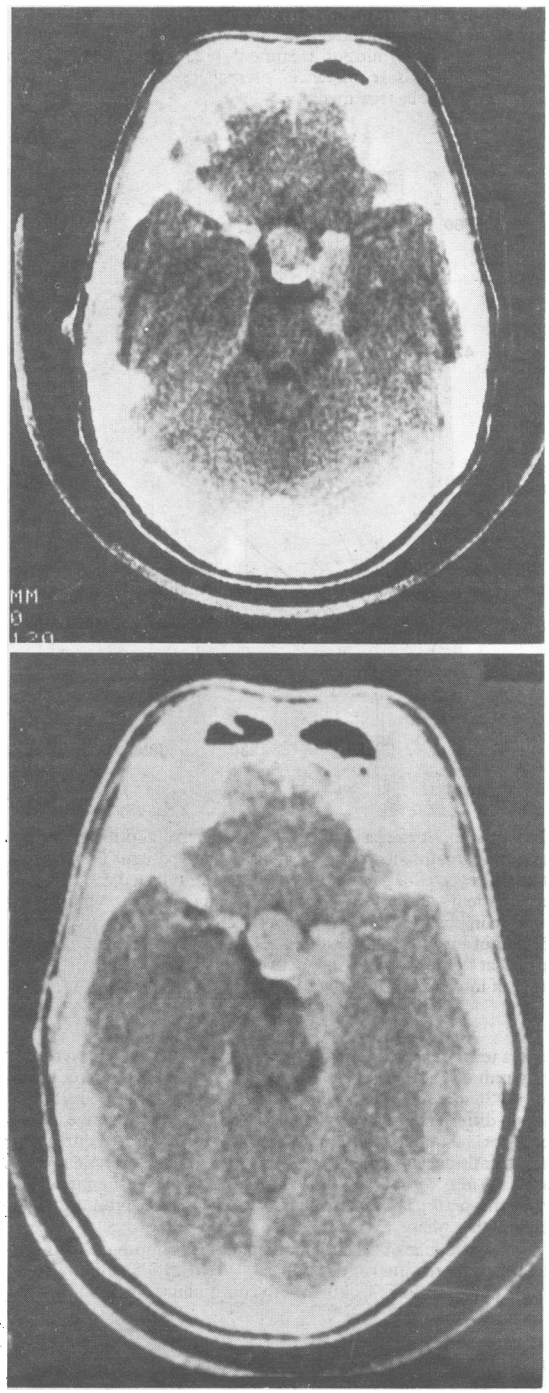
Rapid progression of a growth hormone producing tumour during dopamine agonist treatment

Treatment with dopamine agonists has been tried in patients with growth hormone producing tumours and acromegaly. Most reports show that the concentrations of growth hormone decrease in most patients with acromegaly,[1] but some claim that concentrations decrease only in patients who have shown a modest increase in growth hormone concentrations.[2] According to other authors, dopamine agonists are effective only in patients with acromegaly and hyperprolactinaemia.[3]

We report on a patient with acromegaly and hyperprolactinaemia, in whom treatment with the dopamine agonist bromocriptine caused a rapid progression of the growth hormone producing tumour.

Case report

A 40 year old man had had symptoms of acromegaly for at least 10 years with headache, acral enlargement, thickening of the soft tissue of the face and lips, and hyperhidrosis. Radiography showed an intrasellar pituitary tumour with suprasellar and parasellar extension. The plasma concentration of growth hormone was 180 pmol/l (normal <230 pmol/l), but the patient had detectable growth hormone concentrations throughout the day and night, as reported in other patients with acromegaly and "normal growth hormone concentrations."[4] In addition, a rise in growth hormone concentration after intravenous injection of thyrotrophin releasing hormone was noticed, a common response in patients with acromegaly. The prolactin concentration was increased at 6·8 nmol/l (normal <1·15 nmol/l).



Computed tomograms showing mixed growth hormone and prolactin producing pituitary tumour of patient before (above) and after (below) 10 months of treatment with bromocriptine 10 mg/daily.

Treatment with bromocriptine was tried first because of the high prolactin concentrations together with the "normal" growth hormone concentrations in this patient. Two months after bromocriptine treatment 10 mg daily was started a rise in growth hormone concentration to 3400 pmol/l was noticed. Prolactin concentration decreased during this period to 1·4 nmol/l. Another five months later growth hormone concentration was 16 400 pmol/l and prolactin 0·9 nmol/l.

Radiography showed that the tumour had grown (figure). At this time the patient also developed visual field defects and because of this deterioration was submitted for surgery.