were employed in manufacturing and non-manufacturing work had almost identical rates of abortion, and this relativity was not affected after logistic regression had accounted for differences in age, parity, history of abortion, education, and smoking. Thus there were no important differences between the two groups in these respects.

This study thus provides support for the findings of Clarke and Mason that leatherwork in pregnancy may be associated with an increased risk of stillbirth.¹ The excess was entirely in the previous pregnancies, for which our data were complete and, we believe, reliable. In current pregnancies, in which stillbirths were incompletely ascertained, the absence of excess (one observed against 0.95 expected) is based on numbers too small to be interpreted. The difference between the ratio of observed to expected cases in current and previous pregnancies is no more than can be explained by chance. We did not, however, find any convincing evidence of an increase in fetal malformations. The only type of congenital defect on which Clarke and Mason commented were the three cases of trisomy 18 in an estimated 1200 births, or one in 400. As we had only 346 term pregnancies in leatherworkers and no case of trisomy 18 we are not able to confirm or refute their finding.

There is not necessarily any contradiction in finding a hazard that causes stillbirth and not malformation. A toxic agent acting later in pregnancy even over a short period could kill a fetus, whereas our knowledge of teratology suggests that only an agent acting at the right time in the first trimester might cause a malformation.

The findings of Clarke and Mason and our own suggest that leatherwork may possibly expose women to a fetotoxic agent. We examined the work histories of the eight women in our study whose infants were stillborn; all operated sewing machines, three manufacturing shoes, three bags, and one belts. Five of the eight described exposure to glues (or cements, or both), one to paint, and one to silicone. It seems desirable to investigate the possible fetotoxicity of materials used in the manufacture of leather products.

Reference

1 Clarke M, Mason ES. Leatherwork: a possible hazard to reproduction. *Br Med J* 1985;290:1235-7.

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Remission of symptoms during long term treatment of metastatic pancreatic endocrine tumours with long acting somatostatin analogue

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Abstract

Five patients with metastatic pancreatic endocrine tumours injected a long acting somatostatin analogue (SMS 201-995) 50 µg subcutaneously every 12 hours and were followed up for three to six months. Treatment aimed at controlling excess secretion of hormone by the tumours thereby bringing symptomatic relief.

Four patients showed a significant reduction in tumour related hormone concentrations but in none did values return to normal. All five patients, however, noted definite symptomatic improvement and in one this was dramatic (disappearance of life threatening diarrhoea and correction of metabolic acidosis and hypokalaemia within 48 hours). Mild worsening of symptoms and increasing fasting tumour related hormone concentrations after three to six months of treatment were reversed by doubling the 12 hourly dose. The treatment was well tolerated and had no deleterious effect on fasting blood glucose concentrations.

This somatostatin analogue seems a promising non-invasive treatment for metastatic pancreatic endocrine tumours.

Introduction

Pancreatic endocrine tumours (apudomas), being slow growing malignancies, cause morbidity and mortality by virtue of the excess hormones that they secrete. Most patients have metastases at presentation, and treatment is then palliative. In contrast with many other metastatic malignancies, however, years of symptomatic relief may result if the tumour related hormone excess can be controlled. Current methods of treatment are surgical debulking, arterial embolisation of hepatic metastases, and chemotherapy. Native 14 amino acid somatostatin has been shown to have potent antisecretory properties on these tumours.¹ To be therapeutically useful a long acting and conveniently administered analogue is needed. We report the preliminary results of using such an analogue (SMS 201-995, Sandoz Laboratories, Basle).

Patients and methods

We studied five patients with metastatic pancreatic endocrine tumours. Two patients had tumours secreting vasoactive intestinal polypeptide (vipomas), two had glucagonomas, and one had a tumour producing growth hormone releasing factor. Four of the patients had relapsed after other forms of treatment, while one declined chemotherapy and invasive forms of treatment.

Before starting treatment with SMS 201-995 we assessed the patient's clinical condition, tumour related hormone concentration, blood glucose concentration, and tumour bulk (by computed tomography; CT). The acute tumour related hormone response to a test dose of 50 µg SMS 201-995 subcutaneously was also determined.

Initial treatment was with 50 µg SMS 201-995 given subcutaneously every 12 hours. The patients injected the analogue, using a method similar to insulin injections in diabetics. Full clinical and hormonal evaluation was undertaken every three months. Two patients were followed up for six months and three patients for three months.

Tumour related hormone concentrations were measured by radioimmunoassay.²

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Clinical and hormonal profiles of patients before and after treatment with SMS 201-995

Case No	Age and sex	Diagnosis	Previous treatment	Before SMS 201-995		After SMS 201-995*	
				Clinical state	Mean hormone concentration (SEM)§	Clinical state	Mean hormone concentration (SEM)§
1	44 M	Vipoma	Streptozocin and hepatic arterial embolisation	Severe watery diarrhoea, hypokalaemia, dehydration	VIP 361 (19) pmol/l	Diarrhoea stopped, hypokalaemia and dehydration corrected. Returned to work	VIP 207 (25) pmol/l†
2	57 M	Vipoma	Hepatic arterial embolisation and streptozocin	Watery diarrhoea, weight loss	VIP 120 (2) pmol/l	Diarrhoea stopped, regained weight	VIP 60 (2) pmol/l†
3	70 M	Glucagonoma	None: declined invasive methods	Severe generalised rash, hypoproteinaemia, anaemia	Glucagon 458 (3) pmol/l	Rash subsided, hypoproteinaemia and anaemia improved	Glucagon 364 (4) pmol/l†
4	66 M	Glucagonoma	Hepatic arterial embolisation and streptozocin	Rash on trunk and buttocks; worsening diabetic control	Glucagon 340 (7) pmol/l	Rash subsided, improved diabetic control	Glucagon 332 (7) pmol/l
5	60 F	GRF secreting apudoma	Hepatic arterial embolisation	Acromegaly, sweating, tiredness	GRF 3100 pmol/l; GH 24 (1) mIU/l	Inappropriate sweating stopped	GRF 1200 pmol/l†; GH 8 (1) mIU/l†

*Evaluation after six months' treatment in cases 1 and 5, and after three months' treatment in cases 2, 3, and 4.

†Compared with pretreatment value $p < 0.05$ (Student's *t* test).

‡Single reading.

§VIP=Vasoactive intestinal polypeptide (normal value < 30 pmol/l (< 100 pg/ml)). Glucagon: normal value < 50 pmol/l (< 175 pg/ml). GRF=Growth hormone releasing factor (normal value < 50 pmol/l (< 250 pg/ml)). GH=Growth hormone (normal value < 5 mIU/l).

Results

The table summarises the results. The fasting tumour related hormone concentration fell by at least 60% of basal value after the 50 µg test dose in every case. All patients showed definite symptomatic improvement. In case 1 this was dramatic, with disappearance of life threatening diarrhoea and correction of metabolic acidosis and hypokalaemia within 48 hours of initiating treatment. (This case is reported in detail elsewhere.³) In the other patients clinical improvement started after two to seven days of treatment.

Significantly lower tumour related hormone concentrations were seen after regular treatment with the analogue in four patients. In none of the patients, however, did the hormone concentrations return to normal. One patient (case 4) showed no change of hormone concentrations despite benefiting clinically.

CT showed possible shrinkage of hepatic metastases in case 1, no change in tumour bulk in cases 2 to 4, and a progressive increase in size in case 5. All patients showed mild symptomatic deterioration or increasing fasting tumour related hormone concentrations after three to six months of treatment. These were effectively reversed by increasing the dose of the analogue to 100 µg 12 hourly.

No deterioration of fasting blood glucose concentration (mean 6.26 (SEM 0.32) mmol/l (113.0 (5.8) mg/100 ml) before treatment) was seen after treatment (6.30 (0.59) mmol/l; 114.0 (10.6) mg/100 ml). Apart from local skin irritation during and for a few seconds after injection, long term treatment with SMS 201-995 was well tolerated.

Discussion

This study shows that satisfactory palliation of metastatic pancreatic endocrine tumours can be achieved with SMS 201-995. Our results extend those in two recent case reports of its use in vipomas^{1,4} and show that its effectiveness is not confined to tumours

secreting vasoactive intestinal polypeptide but applies also to other APUD cell neoplasms.

Clinical improvement was rapid with the vipomas, but even with the other tumours response occurred after only one week's treatment, allowing patients with metastatic tumours to lead normal lives at home. The treatment required minimal time in hospital. The improvement in the patients' clinical condition despite the continuing raised hormone concentrations may have occurred because the somatostatin analogue also has a direct effect on the hormone target organ. This may explain the beneficial effect of the somatostatin analogue in some cases of diarrhoea not due to abnormal secretion of vasoactive intestinal polypeptide.⁵

The need to increase the dose after three to six months may be due to mild desensitisation or to progression of tumour. Tachyphylaxis was not a serious problem in this study.

SMS 201-995 appears promising as a safe, effective, and non-invasive treatment for metastatic pancreatic endocrine tumours.

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100 YEARS AGO

It is of course open to argument that at the age of eighteen to twenty-five, a young man should be left a good deal of latitude as to the methods of picking up information, and as to times and periods of study, and that allowance should be made for the development of individual genius and idiosyncrasy and for the tendency of men to give usefully a large amount of time to particular subjects towards which their bent lies. All this, however, could very well be allowed for under any system of check and report; and it is more than probable that the proportion of the social catastrophes and educational failures among medical students might be considerably diminished, if means were taken periodically and systematically to report to their parents or guardians their progress, attendance, and conduct. The proposition is likely to be resented by two classes; by the medical students themselves, who are apt to rate highly a licence which the present system gives alike to the well disposed and to the idlers; and by the school tutors, who from the

multiplicity of medical schools in London and their deficiency in adequate funds, are apt to be overworked and underpaid. The one will resent the system of restriction, and the other will object to the imposition of an irksome and laborious duty. It is not in the nature of young men to welcome restraint; it is not in the nature of teachers willingly to accept responsible and troublesome additions to their task. Nevertheless, it will, we think, be agreed that medical students in London are not at present either so well cared for or so well looked after as in their real interests they ought to be, and that in both respects there is an urgent call for immediate and considerable amendment in our metropolitan system. With Dr. Evatt's objection to the system of what is known as perpetual pupilship, we have less sympathy. It has many advantages, and is founded upon real necessities of student-life, while the disadvantages which he alleges are relatively trifling and unimportant. (*British Medical Journal* 1886;iii:259.)

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