physiology of the pancreas graft, which is heterotopic and denervated, together with the immunosuppressive treatment and relatively impaired renal function might be responsible for minor differences in hormonal and metabolic patterns.

Results comparable to ours have been described in non uraemic type I diabetic patients treated with artificial endocrine pancreas; continuous subcutaneous, intravenous, or intraperitoneal insulin infusions; and intensified conventional insulin treatments.³¹⁻³⁵

Pancreas transplantation seems an ethical proposition in type I diabetic patients undergoing kidney transplantation for chronic renal failure and in whom immunosuppression is to be used. In these cases pancreas transplantation, when successful, leads to the restoration of normal metabolic homeostasis without hormone replacement.

We thank Dr M Seoud El Yafi for help in the care of the patients and Professor Piero P Foa for reviewing the manuscript. This work was supported in part by the Consiglio Nazionale delle Ricerche, Italy (CNR Progetto Finalizzato Malattie Croniche e Degenerative, Sottoprogetto 4, Obiettivo 46), and by the Juvenile Diabetes Foundation, USA (file No 184066).

References

- Sutherland DER. Pancreas and islet transplantation I. Experimental studies. *Diabetologia* 1981;**20**:161-85.
- Sutherland DER. Pancreas and islet transplantation II. Clinical trials. *Diabetologia* 1981;**20**:435-50.
- Lacy PE, Davie JM, Finke EH. Transplantation of insulin producing tissue. *Am J Med* 1981;**70**:589-94.
- Ostman J, Arner P, Groth CG, Gunnarsson R, Heding LG, Lundgren G. Plasma C-peptide and serum insulin antibodies in diabetic patients receiving pancreas transplant. *Diabetologia* 1980;**19**:25-30.
- McMaster P, Gibby OM, Calne RY, et al. Human pancreatic transplantation: preliminary studies of carbohydrate control. *Transplant Proc* 1981;**13**:371-3.
- Sutherland DER, Najarian JS, Greensberg BZ, et al. Hormonal and metabolic effects of a pancreatic endocrine graft. *Ann Intern Med* 1981;**95**:537-41.
- Traeger J, Dubernard JM, Bosi E, et al. Human segmental pancreatic transplantation for the treatment of insulin dependent diabetes. In: Keen H, Legrain M, eds. *Prevention and management of diabetic nephropathy*. London: MTP Press, 1983:221-9.
- Traeger J, Dubernard JM, Pozza G, et al. Influence of immunosuppressive therapy on the endocrine function of segmental pancreatic allografts. *Transplant Proc* 1983;**15**:1326-9.
- Pozza G, Traeger J, Dubernard JM, et al. Endocrine responses of type-1 (insulin-dependent) diabetic patients following successful pancreas transplantation. *Diabetologia* 1983;**24**:244-8.
- Traeger J, Dubernard JM, Pozza G, et al. Functional study of insulin secretion pattern following segmental neoprene-injected pancreatic allograft in insulin dependent (type 1) diabetic recipients. *Horm Metab Res* 1983;suppl 13:63-6.
- Dubernard JM, Traeger J, Neyra P, Touraine JL, Tranchant D, Blanc-Brunat N. A new method of preparation of segmental pancreatic grafts for transplantation: trials in dogs and in man. *Surgery* 1978;**84**:633-9.
- Bergmeyer HU, ed. *Methoden der enzymatischer analyse*. Weinheim: Verlag Chemie, 1974.
- Heding LG. Determination of total serum insulin in insulin treated diabetic patients. *Diabetologia* 1972;**8**:260-6.
- Heding LG. Radioimmunochemical determination of human C-peptide in serum. *Diabetologia* 1975;**11**:541-8.
- Nakagawa S, Nakayama H, Sasaki T, et al. A simple method for the determination of serum free insulin levels in insulin treated patients. *Diabetes* 1973;**22**:590-600.
- Heding LG, Karperska-Czyzykowska T. C-peptide and proinsulin after oral glucose. *Acta Med Scand* 1980;suppl 639:33-6.
- Schlichtkrull J, Munck D, Jersild M. The M-value, an index of blood sugar control in diabetics. *Acta Med Scand* 1965;**177**:95-102.
- Lillehei RC, Simmons RL, Najarian JS, et al. Pancreaticoduodenal allotransplantation. Experimental and clinical experience. *Ann Surg* 1970;**172**:405-36.
- Sutherland DER, Kendall D. Clinical pancreas and islet transplant registry report. *Transplant Proc* 1985;**17**:307-11.
- Sutherland DER, Goetz FC, Najarian JS. Recent experience with 89 pancreas transplants at a single institution. *Diabetologia* 1984;**27**:149-53.
- Traeger J, Bosi E, Dubernard JM, et al. Thirty months' experience with cyclosporin in human pancreatic transplantation. *Diabetologia* 1984;**27**:154-6.
- Dubernard JM, Traeger J, Touraine JL, Malik MC, Martin X, Devonec M. Patterns of renal and pancreatic rejection in double-grafted patients. *Transplant Proc* 1981;**13**:305-7.
- Severyn W, Olson L, Miller J, et al. Studies on the survival of simultaneous canine renal and segmental pancreatic allografts. *Transplantation* 1982;**33**:606-12.
- Traeger J, Dubernard JM, Piatti PM, et al. Clinical aspects of pancreatic rejection in pancreatic and pancreaticorenal allotransplants. *Transplant Proc* 1984;**16**:718-9.
- Traeger J, Dubernard JM, Piatti PM, et al. Cyclosporin in double simultaneous pancreas plus kidney transplantation. *Transplant Proc* 1985;**17**:336-9.
- Blanc-Brunat N, Dubernard JM, Touraine JL, et al. Pathology of the pancreas after intraductal neoprene injection in dogs and diabetic patients treated by pancreatic transplantation. *Diabetologia* 1983;**24**:97-107.
- Di Carlo V, Chiesa R, Pontiroli AE, et al. Intraductal injection of neoprene to suppress native pancreatic exocrine secretion in humans: clinical and metabolic evaluation. *Transplant Proc* 1984;**16**:736-8.
- Calne RY, White DJG, Rolles K, Duffy TJ, Kass T. Renal and segmental pancreatic grafting with draining of exocrine secretion and initial continuous intravenous cyclosporin-A in a patient with insulin dependent diabetes and renal failure. *Br Med J* 1982;**285**:677-80.
- Groth CG, Collste H, Lundgren G, et al. Successful outcome of segmental human pancreatic transplantation with enteric exocrine diversion after modifications in technique. *Lancet* 1982;**ii**:522-4.
- Calne RY. Paratopic segmental pancreas grafting: a technique with portal venous drainage. *Lancet* 1984;**i**:595-7.
- Saibene V, Melandri M, Brembilla L, Spotti D, Pozza G. Comparison between multi-injection and continuous subcutaneous insulin therapy in insulin-dependent diabetic patients. *Acta Diabetol Lat* 1981;**18**:45-50.
- Rizza RA, Gerich JE, Haymond MW, et al. Control of blood sugar in insulin dependent diabetes: comparison of an artificial endocrine pancreas, continuous subcutaneous insulin infusion and intensified conventional insulin therapy. *N Engl J Med* 1980;**303**:1313-8.
- Calabrese G, Bueti A, Santeusano F, et al. Continuous subcutaneous insulin infusion in insulin dependent diabetic patients: a comparison with conventional optimized treatment in a long term study. *Diabetes Care* 1982;**5**:457-65.
- Schiffrin A, Belmonte MM. Comparison between continuous insulin and multiple injections of insulin. A one year prospective study. *Diabetes* 1982;**31**:255-64.
- Pozza G, Spotti D, Micossi P, et al. Long-term continuous intraperitoneal insulin treatment in brittle diabetes. *Br Med J* 1983;**286**:255-6.

(Accepted 11 April 1985)

SHORT REPORTS

Oral cholestyramine increases elimination of warfarin after overdose

Warfarin overdose often requires a long period in hospital because of the prolonged duration of action of the drug. We describe how oral cholestyramine may speed clearance and reduce the period of hospital stay.

Case history

A 25 year old man was admitted one hour after taking an overdose of an unknown amount of warfarin, 10 dextropropoxyphene tablets, and alcohol. He had been run over by a fire engine one year previously and received warfarin for two months for a subsequent pulmonary embolus. Clinical findings were normal but he refused gastric lavage or emesis. His paracetamol concentration was 53 mg/l after four hours and his serum alcohol concentration 37.5 mmol/l (173 mg/100 ml). Liver function values were normal throughout, although his British comparative ratio (international normalised ratio) (BCR) (INR) on admission was 1.3.

He was given vitamin K 10 mg intramuscularly and then oral vitamin K 10 mg daily (figure). Two days later his BCR had risen to 9.2 and he was given a further 10 mg of vitamin K intramuscularly. Oral vitamin K (10 mg) continued to be administered, but after a further two days his BCR had risen to 8.8. Oral cholestyramine (4 g four times a day) was started and vitamin K

(10 mg daily) continued intravenously. His BCR remained between 1.5 and 1.7 for the four days of his hospital stay and he did not develop bruising or bleeding at any time.

Plasma warfarin concentrations were measured by high performance liquid chromatography.¹ The concentration fell log linearly from 13 mg/l six hours after the overdose with a half life of elimination of 53 hours. After cholestyramine the plasma warfarin concentration continued to decline log linearly but with a half life of 33 hours.

Comment

In a report of a patient taking 250 mg warfarin Bjornsson and Blaschke initially administered vitamin K intravenously but then gave oral vitamin K with good response when the prothrombin time rose three days later.² In our patient repeated oral doses of vitamin K (10 mg daily) failed to prevent steep rises in the BCR. Park and co-workers showed that bioavailability of oral vitamin K is low and very variable (10-63%).³ We therefore concur with the recommendations of Bjornsson and Blaschke that vitamin K should be given parenterally,² although we do not agree that it must be given three to five times daily. In our patient a single dose of 10 mg vitamin K parenterally was enough to bring the BCR down within 24 hours on two separate occasions, and this dose given intramuscularly (if the BCR is less than 2.0) or by slow intravenous injection on a twice daily basis should be sufficient in most circumstances. The exact dose and frequency should be governed by the BCR.

We also emphasise the importance of continuing vitamin K until the concentration in the plasma is no longer toxic—that is, normally less than 1 mg/l. In our patient this would have taken around 10 days because of his elimination half life of 53 hours (normal range 20-60 hours).

To our knowledge the effect of cholestyramine on the elimination of warfarin in overdose has not been reported, although its value in phenprocoumon overdose has been shown.⁴ Cholestyramine in-

Plasma warfarin concentrations and British comparative ratios (international normalised ratios) over 10 days after warfarin overdose.

creased plasma warfarin clearance by 30% and reduced elimination half life by a similar amount in five healthy male volunteers given a single intravenous dose of warfarin (1.0-1.2 mg/kg) followed by cholestyramine (4 g three times a day), possibly by interrupting enterohepatic recirculation of warfarin.⁵ We used a larger dose of oral cholestyramine (4 g four times a day) and observed a 38% decrease in elimination half life. Had cholestyramine been administered from the first day the time taken for the plasma warfarin concentration to reach a non-toxic value would probably have been reduced by around 40% and the patient could have been discharged earlier.

We conclude that parenteral vitamin K may have to be continued for several days, but repeated administration of oral cholestyramine should, by increasing warfarin clearance, reduce the time for which this is necessary.

We thank Dr B Spragg, department of clinical biochemistry, for measurement of plasma warfarin concentrations, and the nursing staff of Llandough Poisons Unit for their help.

- 1 Björnsson TD, Blaschke TF, Meffin PJ. High pressure liquid chromatographic analysis of drugs in biological fluids 1. Warfarin. *J Pharm Sci* 1977;66:142-4.
- 2 Björnsson TD, Blaschke TF. Vitamin K disposition and therapy of warfarin overdose. *Lancet* 1978;i:846-7.
- 3 Park BK, Scott AK, Wilson AC, Haynes BP, Breckenridge AM. Plasma disposition of vitamin K in relation to anticoagulant poisoning. *Br J Clin Pharmacol* 1984;18:655-62.
- 4 Meinertz T, Gilfrich H, Bork R, Jahnchen E. Treatment of phenprocoumon intoxication with cholestyramine. *Br Med J* 1977;ii:439.
- 5 Jahnchen E, Meinertz HJ, Gilfrich F, Kersting F, Groth U. Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol* 1978;5:437-40.

(Accepted 22 April 1985)

Llandough Hospital, Penarth, South Glamorgan

S RENOWDEN, MB, BCH, senior house officer
D WESTMORELAND, MB, BCH, house officer
J P WHITE, MB, MRCP, senior registrar
P A ROUTLEDGE, MD, MRCP, consultant physician and senior lecturer in clinical pharmacology

Correspondence to: Dr P A Routledge, Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN.

Smoking habits after laryngectomy

Laryngeal cancer is responsible for about 1% of deaths in the United States and Britain and is predominantly linked to smoking tobacco.¹ Sufferers from other smoking related conditions often continue to smoke regardless.² We have surveyed tobacco smoking among people who have had their larynx removed for laryngeal cancer. Laryngectomy has two potentially important consequences for the smoker, both stemming from the fact that smoke drawn into the mouth cannot be inhaled directly: firstly, further risks to health from smoking should be reduced because the smoke does not reach the lungs; secondly, cigarettes and in some cases pipes or cigars should become less satisfying because of an inability to obtain accustomed concentrations of nicotine from absorption in the lungs.³ The first consequence could lead to smokers continuing to smoke after laryngectomy; the second should work in the opposite direction leading smokers to give up.

Subjects, methods, and results

Smoking questionnaires were distributed to 248 members of laryngectomy clubs and people attending laryngectomy clinics in the United Kingdom. Of the 171 questionnaires completed anonymously and returned (response rate 69%), 145 (85%) were from men. The mean age of the sample was 64 years and the mean time since laryngectomy five years. One hundred and thirty of the respondents (76%) had been current smokers when they sought medical help for their throat condition (see table). The cigarette smokers averaged 28.0 cigarettes a day, the pipe smokers 19.8 g (0.7 oz) of tobacco a day, and the cigar smokers averaged 26.2 a week. Twenty six respondents (15%) were ex-smokers who had given up an average of 14 years previously.

Fifty five of the smokers (42%) continued smoking right up to the time of their laryngectomy. After laryngectomy 52 (40%) of the original smoking sample tried smoking again, of whom 35 (67%) had smoked right up to the time of their operation and 17 (33%) had stopped after seeking help for their throat condition.

The 40% of patients smoking after their laryngectomy had fallen to 19% (25 subjects) by the time of the survey. Most of those who stopped (16/27 (59%)) gave loss of satisfaction as the reason. A further 6 (21%) gave up to avoid further risks to their health, 2 (7%) because they were advised to do so, and 1 (4%) because it was painful. Two patients (9%) gave none of these reasons. Those who were still smoking cigarettes averaged 10.1 a day, considerably less than when their condition was first discovered ($t=15.2$; $p<0.001$). There was no difference in the mean time since laryngectomy between those who were continuing to smoke and those who had given up.

Five laryngectomies reported having tried smoking through their stoma, and one of these continued to do so occasionally.

Numbers of patients smoking cigarettes, pipes, and cigars before and after laryngectomy (total sample=171)

	Before laryngectomy		After laryngectomy	
	On seeking medical help	Just before operation	After operation	At time of survey
Cigarettes only	101	44	32	14
Cigarettes and pipes or cigars	13	4	3	1
Pipes or cigars	16	7	17	10
Total smoking	130	55	52	25