SHORT REPORTS

A misplaced medal? 50 years of unnecessary insulin treatment

The unnecessary treatment of diabetes with insulin has been recognised increasingly.¹ Large doses of insulin may be well tolerated without appreciable hypoglycaemia, for which several mechanisms have been postulated. The development of insulin antibodies may effectively neutralise exogenous insulin, and we describe a diabetic patient treated unnecessarily with insulin in whom this mechanism may have prevented hypoglycaemia.

Case report

In 1927 a 19 year old clerk presented with glycosuria and a history of thirst, polyuria, and weight loss. Diabetes mellitus was diagnosed. There was no family history of diabetes. He was treated with soluble and protamine zinc insulin and subsequently changed to 40 units lente insulin daily. Frequent analysis of urine showed good control.

In 1976 he attended with minor sepsis, and a random blood glucose estimation gave a value of 17.3 mmol/l (312 mg/100 ml). He continued with daily lente insulin, and postprandial glucose values varied from 4.3 to 5.1 mmol/l (77 to 92 mg/100 ml). He had no clinical or biochemical evidence of nephropathy or neuropathy and had minimal background retinopathy with a few scattered microaneurysms and an occasional dot haemorrhage. In 1978 he was awarded the Joslin Gold Medal in recognition of his successful treatment with insulin for more than 50 years.

In 1979 a random plasma C-peptide estimation with antibody M1230² showed an unexpected value of 2.5 nmol/l (7.6 ng/ml), which suggested that he had residual beta cell function. Over the next two months his dose of lente insulin was reduced from 40 to 16 units daily. He remained asymptomatic with no ketonuria and blood glucose values of 4.6-5.4 mmol/l (83-97 mg/100 ml). A glucagon stimulation test (1 mg intravenously) was performed to assess pancreatic and beta cell function and plasma C-peptide values measured before (total C-peptide) and after removal of insulin antibodies from the plasma by acid extraction (free C-peptide). The results (basal C-peptide values: total 0.86 nmol/l (2.6 ng/ml), free 0.64 nmol/l (1.9 ng/ml); 20 minutes after glucagon: total 0.96 nmol/l (2.9 ng/ml), free 0.72 nmol/l (2.2 ng/ml)) confirmed preservation of significant endogenous insulin secretion. One month after withdrawal of insulin an oral glucose tolerance test (50 g) confirmed impaired glucose tolerance (table). This was easily controlled with a carbohydrate restricted diet.

Results of oral glucose tolerance test (50 g) one month after withdrawal of insulin

	Time (min)				
	Fasting	30	60	90	120
Blood glucose (mmol/l)	3.5	8.5	10.3	11.0	8.0
Urinary sugar (%)			0.25		0.5

Conversion: SI to traditional units—Blood glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

During 52 years of insulin administration this patient had never had hypoglycaemia. The presence of circulating insulin antibodies was assessed using a modification of the method of Desbuquois and Aurbach,³ expressing the ratio of antibody bound ¹²⁵I-insulin to total insulin as a percentage. The average percentage binding for our laboratory for a series of patients receiving lente insulin was 19.8%. This patient had a very high titre of antibodies, with a percentage binding of 54%.

Comment

It is apparent in retrospect that this man developed the non-insulin dependent type of diabetes, sometimes known as maturity onset diabetes of youth. In 1927, however, it was assumed that he was insulin dependent, and this would never have been reviewed but for the fortuitous measurement of the plasma C-peptide concentration, which showed underlying pancreatic beta cell function. Surprisingly he had never had hypoglycaemia; this may be explained by neutralisation of the hypoglycaemic effect of exogenous insulin by the high titre of circulating insulin antibodies.

Most patients treated with conventional unpurified bovine insulins develop insulin antibodies. Highly purified insulins are much less immunogenic and conversion from conventional insulins often results in a fall in antibody titre and a reduction in insulin requirement.⁴ Studies in vitro show that insulin bound to antibody does not react

with insulin receptors.⁵ Probably this mechanism allowed our patient to tolerate unnecessary insulin treatment for 50 years.

This case provides a salutary lesson that in certain cases treatment with insulin need not be a life sentence and illustrates the necessity for regular review of the therapeutic management of diabetic patients. We have not dared to ask whether our patient should return his Joslin medal.

We thank Mr R Mohamed, of the immunological unit, University of Aberdeen, for measurement of insulin antibodies, Dr Peter Ashby for the assay of plasma C-peptide, and Miss Lorna Forbes for secretarial help.

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² Heding LG. Radioimmunochemical determination of human C-peptide in serum. *Diabetologia* 1972;8:260-6.

³ Desbuquois D, Aurbach GD. Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol Metab* 1971;33:732-8.

⁴ Walfords S, Allison SP, Reeves WG. The effect of insulin antibodies on insulin dose and diabetic control. *Diabetologia* 1982;22:106-10.

⁵ de Pirro R, Fusco A, Spallone L, et al. Insulin antibodies prevent insulin-receptor interactions. *Diabetologia* 1980;19:118-22.

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Potential hazard of nebulised salbutamol in patients with haemoptysis

Mild haemoptysis is fairly common in bronchiectasis but severe haemoptysis is rare and may be due to hypertrophy of the bronchial arteries, and hence bleeding may occur from the systemic circulation. Selective adrenoceptor agonists such as salbutamol and terbutaline are commonly used as bronchodilators. These drugs, as well as relaxing smooth muscle in the bronchial wall, result in systemic and pulmonary vascular vasodilatation if given intravenously or by mouth.^{2,3} We describe a patient with bronchiectasis in whom nebulised salbutamol apparently increased the degree of haemoptysis.

Case report

A 54 year old woman with known bronchiectasis since the age of 8 was admitted to hospital with a 24 hour history of haemoptysis and a two day history of cough productive of purulent sputum. She gave no history of chest pain and there was no history of tuberculosis. She did not smoke. Clinical examination showed pronounced clubbing of fingers and toes. There was no clinical evidence of deep venous thrombosis. Pulse rate was 90/min, of normal volume and regular, and blood pressure 140/80 mm Hg. In the chest coarse crepitations in the right mid and lower zones and bilateral expiratory rhonchi were heard. Investigations (full blood count) showed a haemoglobin concentration of 14 g/dl with a leucocytosis of $16.4 \times 10^9/l$ (85% neutrophils), a normal platelet count, and normal urea and electrolyte and liver function values. Blood gas analysis showed slightly reduced arterial oxygen pressure only. An electrocardiogram was normal, as was the coagulation screen. A tine tuberculin test elicited a grade 1 response. Peak expiratory flow rate was 120 l/min, forced expiratory volume in one second (FEV₁) 1.5 l, forced vital capacity (FVC) 3.0 l, and FEV₁:FVC ratio 50%. Her drug treatment consisted of salbutamol and ipratropium inhalers two puffs four times daily each. She had been shown to have 15% improvement in ventilatory function after isoprenaline.

On admission treatment was instituted with an antibiotic and nebulised salbutamol 5 mg six hourly (dose and method of administration of salbutamol routinely used in our patients admitted with reversible airflow obstruction). The patient continued to have intermittent haemoptyses varying between 50 and 450 ml. Her haemoglobin concentration dropped to 10 g/dl within

week. We noticed that large haemoptyses occurred shortly after the nebulised salbutamol. After substitution of the salbutamol by nebulised isotonic saline there was a pronounced reduction in haemoptysis with only streaks of blood in the sputum thereafter. To substantiate these observations nebulised salbutamol was reintroduced and caused a further large haemoptysis (300 ml). Bronchodilator treatment was therefore subsequently maintained with oral prednisolone and the nebulised salbutamol discontinued. The episodes of haemoptysis gradually subsided over the next 48 hours. There was no recurrence when inhaled salbutamol 200 µg four times daily was reinstituted one week later.

Comment

Although intermittent haemoptysis may occur in bronchiectasis and be exacerbated by intercurrent infection, in our patient the continued use of nebulised salbutamol appeared to increase the degree of haemoptysis. This effect may be dose related, since before admission and during two previous admissions for haemoptysis the patient had used a salbutamol inhaler 200 µg four times daily as well as an ipratropium inhaler without any apparent adverse effect. During the two previous admissions when nebulised salbutamol was not used the haemoptysis was much less severe, less persistent, and disappeared within 48 hours. We therefore suggest that nebulised salbutamol and other similar nebulised drugs should be used with caution in patients with chronic reversible airflow obstruction and haemoptysis.

Neither Allen and Hanburys Ltd nor the Committee on Safety of Medicines had any record of this side effect of nebulised salbutamol being notified to them.

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Exacerbation of chronic liver disease due to hepatitis B surface antigen after delta infection

Carriers of the hepatitis B surface antigen (HBsAg) appear to be at high risk of developing δ infection.¹ The δ agent is highly pathogenic and causes acute and chronic liver disease.² δ Antigen is detectable in serum only in acute hepatitis and indicates recent δ infection³; in chronic hepatitis δ antigen may be identified in liver specimens, but in the serum only the antibody to it (anti- δ) may be identified.⁴ Results of recent studies⁵ suggests that the δ agent is a factor in fulminant hepatitis in asymptomatic carriers of HBsAg; it could also be responsible for serious infections in patients with chronic HBsAg liver disease.

We report on three patients with a history of chronic HBsAg liver disease whose clinical condition worsened suddenly and who died; sera from the three patients were tested for the presence of markers of hepatitis B virus and the δ agent.

Patients, methods, and results

We examined three men admitted to hospital with jaundice. Their histories showed them to have been HBsAg carriers for at least two years with raised activity of alanine transaminase (from two to four times normal), slightly raised bilirubin concentration, serum albumin concentration >30 g/l, and gammaglobulinaemia <20 g/l. They had not had ascites, bleeding, or periods of disturbed consciousness. Only one had undergone liver biopsy: histology had shown chronic persistent hepatitis. None had had previous treatment, and none was alcoholic.

During admission alanine transaminase activity was three to five times normal and they had hyperbilirubinaemia (six or more times normal concentrations), low serum albumin concentrations, hypergammaglobulinaemia,

prolonged prothrombin times, ascites, bleeding, and disturbed consciousness progressing to hepatic coma. Death occurred three to five weeks after admission.

Sera of the three patients were tested for markers of hepatitis B virus and δ agent. HBsAg, antibody to HBsAg (anti-HBs), total antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe) were estimated with commercial radioimmunoassays (Ausria II, Ausab, Corab, Kit HBe; Abbott, Chicago, Illinois). Anti-HBc of IgM class (IgM anti-HBc) was detected with a solid phase radioimmunoassay using the method described by Lavarini *et al*⁴ (the HBe reagent was kindly provided by Dr Rizzetto, and we used anti-HBc iodine-125 from kit Corab, Abbott). Serum δ antigen and anti- δ were detected with solid phase enzyme linked immunosorbent assay based on the technique described by Crivelli *et al*⁵ (IgG anti- δ conjugated with immunoperoxidase was kindly provided by Dr Rizzetto).

The three patients were positive for HBsAg, total anti-HBc, and anti-HBe and negative for anti-HBs, IgM anti-HBc, and HBeAg; they were positive for δ antigen and negative for antibody to it.

Comment

The δ agent is highly pathogenic; in asymptomatic carriers of HBsAg it usually produces acute hepatitis that can occasionally be fulminant and often becomes chronic. In the three cases described the δ agent did not produce the classical picture of acute hepatitis with very high alanine transaminase activity. The patients in fact had suffered for at least two years from an HBsAg hepatitis that had evolved slowly, as is usually observed in our area, and then their condition deteriorated unexpectedly, leading to death. The infection with hepatitis B virus was not recent since their sera were positive for anti-HBe and negative for IgM anti-HBc; the presence of δ antigen in the sera indicated current infection by the δ agent.

We therefore presume that in these three cases the δ agent played an important part in the sudden and fatal exacerbation of the patients' liver disease.

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⁴ Lavarini C, Crivelli O, Smedile A, *et al*. Radioimmunoassay detection of IgM antibodies to the hepatitis B core antigen in HBsAg liver disease. *Boll Ist Sieroter Milan* (in press).

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Chlormezanone poisoning

Chlormezanone is a tranquilliser with muscle relaxant properties that was first introduced into clinical practice in 1958. There is, however, only one published report of an overdose due to this drug.¹ We report a further case of chlormezanone intoxication.

Case report

A 36 year old woman was admitted to hospital after ingesting 7 g chlormezanone (Trancopal) five hours previously. On admission she was comatose (grade 3, Edinburgh scale) and hypotensive (95/60 mm Hg) and had a positive gag reflex, equal and reactive pupils, normal fundi, flaccid muscle tone, and reflexes that were generally difficult to elicit. Over the next 15 hours she regained consciousness and her blood pressure rose to 115/70 mm Hg. No evidence of respiratory depression was observed, and renal and hepatic function remained normal. The patient made an uneventful recovery.

The figure shows plasma chlormezanone concentrations, estimated by a