Allergy to purified bovine, porcine, and human insulins

We report a case of local and generalised allergy to highly purified insulins that persisted despite change to human insulin.

Case report

A 44 year old non-atopic man was diagnosed as being diabetic in 1978 and started insulin treatment in April 1981 with once daily Lentard (highly purified bovine and porcine insulin). Five days later he noticed local itchy weal and flare reactions lasting one to two hours. Insulin was stopped after six weeks.

In March 1982 once daily Actrapid and Monotard (highly purified porcine insulins) were introduced. After his second injection local reactions reappeared and persisted despite oral prednisolone. On 1 April 1982 he experienced generalised itching, sweating, vomiting, dizziness, and collapse three minutes after an injection. Previous injection sites became red, swollen, and indurated. He was hypotensive but not hypoglycaemic. Insulin was stopped. Thirst, polyuria, and ketonuria returned and twice daily Humulin S (recombinant human insulin) was started two days later as previous prick tests with human insulin had shown no reactions. Prick tests three days later showed immediate local reactions to all commercially available insulins including: recombinant human insulin (Humulin S, Humulin I) (weal size at 10 minutes 1-3 mm); semisynthetic human insulin (Actrapid human) and highly purified porcine insulins (sodium pork insulin (Eli Lilly), Actrapid, monotard) (weal sizes 4-6 mm); and highly purified bovine insulins (Neusulin, Neuphane, Actrapid beef (Novo Laboratories) and histamine (weal sizes 6-9 mm). There was no reaction to any diluent, isopropyl alcohol, zinc sulphate, or control solutions. Prednisolone was stopped.

IgG insulin binding during illness

Date	IgG insulin binding (μg/l)		
	Bovine insulin	Porcine insulin	Human insulin
2 April	9·6	11·4	2·6
30 April	40·8	17·9	8·2
28 May	34·9	14·4	8·4

His condition improved and he gained weight, but local immediate and delayed reactions again became troublesome and in May he suffered a wheezing episode associated with redness and induration at previous injection sites shortly after an injection of Humulin S. Addition of dexamethasone 0·05 mg/injection satisfactorily suppressed the reactions. Three months later the local reactions had disappeared and dexamethasone was reduced and stopped. He remained well.

Investigations—Full blood count was normal (eosinophils 3% of $8·9 \times 10^9$/l) and total serum IgE concentrations on 30 April was 18 U/ml (Pharmacia PRIST method, normal < 120 U/ml). Insulin specific IgE was exceptionally high at 26 U/ml.[1] IgG insulin antibodies were measured as previously described.[2] Before human insulin was started his serum showed appreciable binding for purified bovine and porcine insulins with little reactivity against human insulin (table). Samples taken after prick testing showed a pronounced rise in insulin antibody levels with a preferential binding to bovine insulin.

Comment

The cause of insulin allergy and nature of the antigen remain obscure. Our patient was not allergic to zinc or the insulin diluents and had never received protamine insulins. He received only purified insulins but mixtures of bovine and porcine insulins may have greater antigenicity than either alone.[3] Although initially unreactive, he subsequently reacted to human insulin. Allergic reactions to purified insulins (and human insulin) have been observed but only after previous exposure to conventional insulins.[4] Generalised reactions are uncommon and usually now seen only on reintroduction of insulin after a previous short course.[3]

The relation between circulating insulin antibodies and insulin allergy remains unclear. A proportion, but not all, of those receiving insulin develop insulin antibodies[2 3]; few, however, show allergy or resistance. Patients with generalised insulin allergy have high concentrations of insulin specific IgE (1·0-18·4 U/ml), which is independent of total IgE and insulin specific IgG[1]; such high concentrations have not been recorded in patients with local insulin allergy alone. The pronounced rise in our patient's IgG insulin antibodies with preferential binding to bovine insulin implies recent exposure to bovine insulin. He received no bovine insulin other than during skin testing. His allergy may thus have been exacerbated by the bovine insulin used for skin testing, which emphasises that skin testing is not without risk.

Although our patient showed hypersensitivity to human insulin, the reaction was less than that to other insulins. The use of human insulin, with or without low dose dexamethasone, may be useful in the management of insulin allergy.

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Cardiac arrest after crush injury

The features of the crush syndrome were described during the second world war.[1] Although severe crush injuries are uncommon in civilians, anecdotal reference has been made to sudden death after release from severe crushing.[2] We report a case of cardiac arrest and successful resuscitation one hour after release from prolonged crushing and suggest that biochemical abnormalities may be a cause of sudden death after release from severe prolonged crushing.

Case report

A 47 year old man was crushed when three floors of a derelict tenement building collapsed. Extrication was slow because of the danger of further falls of masonry. He was trapped by a large mass of debris, and only the head, right arm, and shoulder were exposed. He was fully orientated, his pulse was 90 beats/min, and ventilation was adequate. Morphine was given via an intravenous infusion, according to the amount of pain experienced. Oxygen was given by face mask, and 500 ml physiological saline and 500 ml polygeline (Haemaccel) were given intravenously over four hours. He was released after eight hours. There were no obvious major injuries. Blood pressure was 90 mm Hg systolic and pulse 100 beats/min. Further examination in the accident department showed two fractured ribs and compression marks on both legs; he had no other injuries. The foot pulses were easily palpable.

Arterial blood gas tensions just before cardiac arrest, which occurred one hour after release from crushing, were: pH 7·15, oxygen 15 kPa (113 mm Hg), carbon dioxide 4·7 kPa (35 mm Hg) and base excess −17 mmol(mEq)/l. Resuscitation converted ventricular fibrillation to a supraventricular tachycardia with an adequate cardiac output, and the acidosis was treated with 300 mmol(mEq) sodium bicarbonate intravenously. Blood was taken for estimation of electrolyte concentrations, and 15 minutes later he became asystolic. While resuscitation was in progress the electrolyte results became available as follows: sodium concentration 132 mmol(mEq)/l, potassium 8·0 mmol(mEq)/l, chloride 104 mmol(mEq)/l; bicarbonate 11 mmol(mEq)/l; and urea 8·5 mmol/l (51 mg/100 ml). Administration of 50 ml 50% dextrose with 10 units soluble insulin and resuscitation successfully restored sinus rhythm, with normal blood pressure, and spontaneous breathing. Electrocardiography showed peak T waves but no widening of the QRS complexes. The serum potassium concentration fell steadily over the next two hours to 5·0 mmol/l, and apart from a focal seizure no untoward incidents occurred in the first 24 hours.

The legs became swollen with patchy anaesthesia and reduced movement, but the dorsalis pedis pulses remained easily palpable. Qualitative urine analysis confirmed the presence of myoglobinuria. Over the following 48 hours the urine output fell and serum urea concentration rose and he developed progressive respiratory and renal failure. He was treated by intermittent positive pressure ventilation with positive end expiratory pressure for four days and haemodialysis for four weeks. He made a good recovery, and on review at five months his residual deficit was bilateral foot drop and a left radial nerve palsy.

Comment

The pathophysiology and management of the crush syndrome have been extensively reviewed,[3 4] with most case reports emphasising the shock and renal failure. Brown and Nicholls reported serum potassium concentrations of 6·3 and 8·8 mmol/l soon after admission in two patients with severe crush injury. Early rises in serum potassium concentration and early acidosis are probably due to the release of the cation and fixed acids from damaged muscle rather than to any impairment of renal function. Our patient developed classic symptoms of the crush syndrome, but early metabolic changes were more immediately life threatening. These metabolic changes may be the cause of the sudden death that occurs soon after rescue in crushed patients. Lightweight portable electrocardiographic monitors may permit recognition of hyperkalaemia at an early stage in victims of crushing. If no such diagnostic facilities are available it should be remembered that cardiac arrhythmias occurring at an early stage after release from prolonged crushing may be due to hyperkalaemia and acidosis.

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Side effects of thyrotrophin releasing hormone

Bolus injections of thyrotrophin releasing hormone are widely used for studying endocrine disorders. The test has been considered to be relatively free of side effects, but we report four cases in which serious symptoms developed.

Case reports

The thyrotrophin releasing hormone test has been performed on 1500 patients in our departments over the past 10 years. The test is carried out with 400 μg thyrotrophin releasing hormone (Roche, Basle, Switzerland) either alone or in combination with 100 μg gonadotrophin releasing hormone (Hoechst AG, Frankfurt, West Germany) injected over two minutes. Serious side effects developed in four patients (table).

Symptoms observed after thyrotrophin releasing hormone test

Case No	Hormone injected	Symptoms		
		Unconsciousness	Convulsions	Fall in blood pressure
1	TRH and GnRH	+	+	+
2	TRH	+	−	+
3	TRH	−	+	−
4	TRH and GnRH	+	+	not measured

TRH = thyrotrophin releasing hormone.
GnRH = gonadotrophin releasing hormone.

Case 1—A 53 year old man with suspected secondary hypothyroidism after a head injury was given an injection of thyrotrophin releasing hormone and gonadotrophin releasing hormone, and about five minutes later he lost consciousness. His blood pressure fell and for a few minutes was unmeasurable. His pulse rate was 80 beats/minute, and he had general tonic convulsions. He regained consciousness after about five minutes and had completely recovered by the next day. Subsequent electroencephalographic and neurological examinations yielded normal results.

Case 2—A 63 year old man with persistent atrial fibrillation and a history of head injury was given an injection of thyrotrophin releasing hormone to investigate a suspected relapse of primary hyperthyroidism. Between five and 10 minutes after the injection he lost consciousness for about five minutes and his blood pressure fell slightly (100/65 mm Hg). His pulse was normal. Convulsions did not occur, and an electrocardiogram taken 10 minutes later was unchanged. He recovered completely after three hours.

Case 3—A 67 year old woman, admitted with suspected primary hypothyroidism, was given an injection of thyrotrophin releasing hormone, and about 10 minutes later general tonic convulsions occurred, although she did not become unconscious. Her blood pressure was 150/90 mm Hg, and the electrocardiogram showed sinus tachycardia with a heart rate of 120 beats/minute. Diazepam (Vival) 15 mg was given intravenously, which had an immediate effect on the convulsions. By the next day she had recovered completely.

Case 4—A 32 year old man with hypogonadism (Klinefelter's syndrome) lost consciousness two minutes after an injection of thyrotrophin releasing hormone and gonadotrophin releasing hormone, and clonic convulsions occurred for two to three minutes. His blood pressure was not measured, but his pulse was normal (76 beats/minute).

Comment

Vasovagal syncope cannot be excluded in any of these cases, but it usually occurs within one to two minutes, whereas the reactions in our patients occurred two to 10 minutes after injection. As such serious side effects have not been reported with gonadotrophin releasing hormone and as thyrotrophin releasing hormone was the only drug given in two cases we believe that thyrotrophin releasing hormone might be responsible for these side effects.

Convulsions occurred in three out of four patients. Tonic clonic convulsions have been observed in an epileptic patient after intravenous injection of thyrotrophin releasing hormone 500 μg,[1] and Grussendorf *et al*[2] reported side effects similar to those seen in our patients in four patients after injection of thyrotrophin releasing hormone and gonadotrophin releasing hormone (200 μg and 100 μg respectively). Thyrotrophin releasing hormone has several effects on the central nervous system.[3 4] Three of our patients and all of those previously described had either suffered prior cerebral trauma or had cerebral or pituitary damage or dysfunction. About 7% of our patients who did not suffer the same reaction, however, had had previous head injuries of some kind.

It is not known whether the dose of thyrotrophin releasing hormone is important in the aetiology of these side effects, but this is likely. We therefore recommend a standard dose in the thyrotrophin releasing hormone test of 200 μg, which gives sufficient release of thyroid stimulating hormone and prolactin. Moreover, in view of the serious complications that may arise after injection of thyrotrophin releasing hormone greater consideration should be given to whether there is a need for such a test.

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