

infection, which had initially been based on the chorionic villus biopsy examination. The table gives a comparison of the results obtained from the samples taken before and after termination of pregnancy.

Discussion

The vaccination programme carried out in the United Kingdom has not yet eliminated congenital rubella, and therapeutic abortion on the grounds of detection of maternal rubella specific IgM remains the most practical, though not always the most desirable, means of control. Detection of virus specific IgM is not always possible, however, if the time since infection is too great.

Moreover, detection of maternal rubella specific IgM cannot always solve the problems encountered in the diagnosis of congenital rubella. In this case the time of conception could only be imprecisely dated as the first day of the patient's last menstrual period. Thus the time of conception in relation to the acute episode of rubella infection was not clear, and the probability of fetal infection was difficult to assess. In addition, the patient was reluctant to have her pregnancy terminated. A direct measure of fetal infection was desirable, and in this patient a chorionic villus biopsy examination provided the confirmation that was sought. The size of the biopsy specimen obtained was small; evidence of rubella infection was possible only with the sensitive and highly specific immunoblot and hybridisation tests for rubella virus recently developed in our laboratory. These tests can provide results within three days. Although at this stage the techniques may not be suitable for use in routine diagnostic laboratories because of the requirement for ^{125}I and ^{32}P radioactivity, these difficulties will be overcome when non-radioactive labels of comparable sensitivity become available.

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SHORT REPORTS

Generalised allergic reaction to human insulin

I report a case of local and generalised allergy to Human Monotard insulin that did not recur with transfer to highly purified bovine insulin.

Case report

A 71 year old woman had been an insulin dependent diabetic for 50 years without any history of allergy. Since 1971 her diabetes had been well controlled by neutral insulin (Neusulin) and semilente/lente insulin (Neulente). In September 1983 an infection in her left foot led to amputation of the fifth toe. Her diabetes was well controlled throughout this episode. She was readmitted to hospital in January 1984, having hit her left foot during a fall caused by hypoglycaemia; by 8 February gangrene was apparent in the fourth toe. Her regimen of highly purified Neusulin and Neulente was changed to a sliding scale of Human Actrapid, of which she required 40 units a day. The gangrene deteriorated and on 23 February her left leg was amputated below the knee. After surgery her insulin requirements decreased, and by 13 March she was better and her wound had healed well; she was receiving 12 units of Human Actrapid three times daily. On 19 March she started taking Human Monotard 14 units in the morning and Human Actrapid 10 units twice daily. Two days later she developed a severe eczematous urticarial rash with itching on both upper arms, both legs, the chest, neck, and face. She was mildly feverish (temperature 37.2°C) but did not have associated dyspnoea or wheezing. Treatment was continued, and the next day the rash increased in size, becoming more confluent and remaining intensely pruritic. Its allergic nature was confirmed by a consultant dermatologist,

and the Human Monotard was stopped but the Human Actrapid continued. Over the next 10 days the rash resolved and she was transferred to her original regimen of Neusulin and Neulente before being discharged.

In prick tests performed after her discharge she did not respond to the following insulins (one unit in 1 ml of physiological saline): Neulente, Semitard, Ultratard, human isophane, Human Protaphane, Semitard MC, protamine zinc, and Human Actrapid. She did not respond either to zinc acetate or to the diluents used for Human Actrapid and Human Monotard, but doses of 0.1 ml of one unit of Human Monotard in 1 ml of physiological saline produced large wheal and flare reactions visible for several hours afterwards.

Investigations—A full blood count showed: haemoglobin 129 g/l, leucocyte count $11.3 \times 10^9/\text{l}$ (85% neutrophils, 10% lymphocytes, 4% eosinophils), erythrocyte sedimentation rate 23 mm in the first hour, platelets $325 \times 10^9/\text{l}$. On readmission insulin specific IgE was below the limit of detection (0.2 U/ml) and insulin specific IgG concentration was 0.204 mU/ml .

Comment

Generalised and local reactions to purified and human insulin have been observed^{1,2}; these usually occur after previous exposure to conventional insulins, though cases without previous exposure have been described.³ Wheal and flare reactions to testing are also recognised as a dermal hypersensitivity reaction to insulin.⁴ Patients with generalised insulin allergy usually have high concentrations of insulin specific IgE, but this does not seem to occur with local reactions to insulin.⁵ The mechanism of this patient's reaction remains unclear because it did not occur with Human Actrapid or highly purified bovine insulin and therefore cannot have been a straightforward allergy to insulin. It seems that human insulins, though

promoted as being less allergenic than animal insulins, nevertheless carry a risk of allergic reactions. To my knowledge, this is the first reported case of a generalised allergic reaction to human insulin in which reactions to highly purified monocomponent bovine and porcine insulins did not also occur.

I thank Dr S Haider for permission to report this case, Dr J S Kristenson (Novo Research Institute, Bagsvaerd, Denmark) for the determination of insulin specific IgE and IgG, Novo Laboratories Ltd for providing the allergy testing kit, and Mrs V Jones for typing the manuscript.

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Gravesend and North Kent District General Hospital, Gravesend, Kent DA11 0DG

P SILVERSTONE, MB, BS, senior house officer

Correspondence to: Medical Unit, East Surrey Hospital, Redhill, Surrey.

Is there a link between iritis and diabetic autonomic neuropathy?

The strong association reported between iritis and autonomic neuropathy in insulin dependent diabetics has been used to support the hypothesis that damage to the autonomic nervous system is immunologically mediated.¹ The high prevalence of iritis found in diabetics in that study ran counter to our own clinical experience, and we therefore investigated the prevalence of the condition in patients attending the diabetic department of this hospital.

Patients, methods, and results

Tests of autonomic function² had been performed on 385 diabetics over three years. All the diabetics, except 17 known to have died, were sent a questionnaire to elicit the relative prevalence of iritis in the groups with and without autonomic neuropathy. The questionnaire asked about painful eye conditions requiring medical consultation. We followed up a positive response by contacting the ophthalmologist or general practitioner who had seen the patient and by reviewing the medical records. We also examined the ophthalmological and diabetic records of patients who had died to ascertain whether they had had iritis.

Numbers of diabetics with iritis

	Autonomic function	
	Abnormal	Normal
Diabetics who replied to questionnaire	153	163
Definite iritis	3*	1
Undiagnosed eye condition	2	
Diabetics who had died	16	1
Definite iritis	1†	
All diabetics	169	164
All possible cases of iritis	6	1

*One case occurred after removal of a cataract.

†Occurred after exposure to ultraviolet light.

The questionnaire was validated by sending it to non-diabetic patients who had attended the ophthalmology department from 1980 to 1983 with a single uncomplicated episode of iritis. Of the 14 who replied, 13 responded positively to the question about a painful eye condition.

Of the 316 diabetic patients who returned the questionnaire (response rate 86%), 33 reported a painful eye condition. Only four of these had had iritis; one had developed the condition immediately after removal of a cataract. In 27 cases we obtained a definite diagnosis of a condition other than iritis, and in two we were unable to make a diagnosis. The records of patients who had died showed one case of iritis, which had probably been caused by exposure to ultraviolet light

during welding. The table summarises the results. Even when the two patients without definite diagnoses and the two patients with recognised causes of their iritis were included the prevalence of iritis in the group with autonomic neuropathy was less than 4%. This was not significantly higher than that in the group with normal results of tests of autonomic function ($p=0.13$, Fisher's exact test).

In the original report 47 diabetics aged 40 or less, all insulin dependent, had autonomic neuropathy as defined by a heart rate variability less than 10; 14 gave a history of iritis.¹ We identified 28 patients in our sample who fulfilled exactly these criteria; only one gave a history of iritis.

Comment

Iritis was strikingly less common in our patients with autonomic neuropathy than in those described by Guy *et al.*¹ This was true even when the analysis was confined to patients who met the same criteria of age, insulin dependence, and abnormality of heart rate variation. We did not find iritis to be significantly more prevalent in patients with autonomic neuropathy than in patients with normal autonomic function, but the uncertainty surrounding the estimate of the odds ratio, calculated using cases of definite iritis without recognised cause (odds ratio=2, 95% confidence limits 0.2, 22), means that our data do not exclude an association between the two conditions.

Unusual patients tend to be referred to specialised clinics.³ Perhaps the reputation of Guy *et al* for research into diabetic neuropathy led them to study an atypical group of patients. Our failure to replicate their finding, in a large sample of patients, of a high prevalence of iritis in diabetics with autonomic neuropathy must reduce the strength of their evidence for an immune pathogenesis for diabetic autonomic neuropathy.

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University Department of Medicine and Diabetic Department, Royal Infirmary, Edinburgh EH3 9YW

C N MARTYN, DPHIL, MRCP, lecturer

R J YOUNG, BSC, MRCP, senior registrar

D J EWING, MD, FRCP, Wellcome Trust senior lecturer

Correspondence to: Dr C N Martyn, MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO9 4XY.

Effects of indomethacin and sulindac on blood pressure of hypertensive patients

Some studies,^{1,2} but not others,³ have shown a pressor effect of indomethacin in patients treated for hypertension. Sulindac selectively inhibits extrarenal synthesis of prostaglandin and may not, therefore, antagonise the action of antihypertensive drugs.^{4,5} In an observer blind study we compared the effects of indomethacin and sulindac on blood pressure and symptoms in hypertensive patients who needed treatment with a non-steroidal anti-inflammatory drug.

Patients, methods, and results

Twenty one patients with hypertension and coexisting joint disorders requiring treatment with a non-steroidal anti-inflammatory drug consented to the study, which was approved by the hospital ethics committee. They comprised 12 women and nine men (mean age 62 (range 40-76), mean weight 80 (56-108) kg). The antihypertensive drugs taken were kept constant throughout the study. Mean blood pressure on entry to the study was 147/95 mm Hg lying and 135/98 mm Hg standing. The open crossover study, with three phases, compared indomethacin (50 mg twice daily), sulindac (200 mg twice daily), and paracetamol (1 g four times daily); the order of treatments was varied using Williams squares. Phases of treatment lasted six weeks unless they had to be shortened because of side effects or unsatisfactory relief of symptoms. There were no washout intervals. Paracetamol was used instead of placebo because all patients required treatment for symptoms. Blood pressure, body weight, scores for pain and stiffness (10 cm