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 Kristensen (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. 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 function 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.

<table>
<thead>
<tr>
<th>Numbers of diabetics with iritis</th>
<th>Autonomic function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abnormal</td>
</tr>
<tr>
<td>Diabetics who replied to questionnaire</td>
<td>153</td>
</tr>
<tr>
<td>Definite iritis</td>
<td>1*</td>
</tr>
<tr>
<td>Undiagnosed eye condition</td>
<td>2</td>
</tr>
<tr>
<td>Diabetics who had died</td>
<td>16</td>
</tr>
<tr>
<td>Definite iritis</td>
<td>1</td>
</tr>
<tr>
<td>All diabetics</td>
<td>169</td>
</tr>
<tr>
<td>All possible cases of iritis</td>
<td>6</td>
</tr>
</tbody>
</table>

*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 diabetics who returned the questionnaire (response rate 86%), 33 reported a painful eye condition. Only four of these had had iritis; one had died and 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. We identified 28 patients in our sample who fulfilled exactly these criteria; one only 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. 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. 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.

We are grateful to Drs L Duncan, B F Clarke, and A Adams for allowing us to study their patients and to Kate Henderson and Carol O'Neill for help in collecting the data.

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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, but not others, 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. 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
Mean (and range) results for patients who completed two weeks of treatment with all three drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lying (mean arterial pressure: mm Hg)</th>
<th>Standing (mean arterial pressure: mm Hg)</th>
<th>Body weight (kg)</th>
<th>Pain score (mm)</th>
<th>Stiffness score (mm)</th>
<th>Reasons for stopping:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>103-8 (81-120-0)</td>
<td>109-9 (87-138-8)</td>
<td>81.4-5 (62-108.8)</td>
<td>63 (25-98)</td>
<td>67 (6-98)</td>
<td>Poor symptom relief</td>
</tr>
<tr>
<td></td>
<td>102-4 (78-123-6)</td>
<td>106-8 (91-138-6)</td>
<td>81.5-5 (56-109-5)</td>
<td>49 (20-95)</td>
<td>54 (12-97)</td>
<td>Side effects</td>
</tr>
<tr>
<td>Sulindac</td>
<td>109-7 (102-6-152-0)</td>
<td>116-4 (99-3-133-8)</td>
<td>81-7 (56-108-5)</td>
<td>46 (8-82)</td>
<td>48 (7-98)</td>
<td>Total</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>108-1 (101-6-151-0)</td>
<td>117-8 (101-2-152-0)</td>
<td>81-5 (56-109-5)</td>
<td>49 (20-95)</td>
<td>54 (12-97)</td>
<td></td>
</tr>
</tbody>
</table>

*Significance of difference among all three treatments by analysis of variance or χ² test with Yates’s correction.

**Antithrombin III concentration, thrombosis, and treatment with luteinising hormone releasing hormone agonist in prostatic carcinoma**

Treatment of advanced carcinoma of the prostate is based mainly on the assumption that the tumour is androgen dependent. In the past oestrogens have been used most commonly as endocrine treatment. Serious exacerbation of thromboembolic complications during oestrogen treatment, however, prompted investigation of alternative means of androgen suppression. In 1980 Tolis et al showed that testosterone could be suppressed by giving agonists of luteinising hormone releasing hormone, which might thus be used instead of oestrogens. The mechanism of the thrombogenic effect of oestrogens is unclear, but recent studies suggested that all the effects of blood clotting induced by oestrogen treatment of prostatic cancer, the fall in plasma antithrombin III concentration is the most important.

Before agonists of luteinising hormone releasing hormone are introduced as endocrine treatment for prostatic cancer it is essential to establish whether they influence clotting in the same way as oestrogens. We therefore measured antithrombin III concentrations in patients with carcinoma of the prostate before and during treatment with the luteinising hormone releasing hormone agonist IC1 118.630 depot to estimate the risk of thromboembolic events.

**Patients, methods, and results**

Thirty men aged 55-84 (mean 72) with cytologically confirmed carcinoma of the prostate were included in the study. All had locally advanced disease or distant metastases, or both. None had previously received endocrine treatment. An agonist of luteinising hormone releasing hormone (IC1 118.630 depot; 3-6 mg) was injected into the skin of the anterior abdominal wall at intervals of 28 days. The plasma concentration of antithrombin III was measured by a technique that uses the chromogenic substrate S-2238 (Kabi Diagnostica, Molndal, Sweden); the normal range for adults is 80-120%. Samples were taken one day before and one, two, and three months after the start of treatment. The endocrine effect of the treatment was assessed by repeated determination of plasma testosterone, luteinising hormone, and follicle stimulating hormone concentrations. The significance of mean differences in values during treatment compared with the baseline values was determined by Fisher’s test.

The mean baseline concentrations of antithrombin III were within the normal range at 103-23 (SD 14-18%). No significant change took place during treatment, the concentrations one, two, and three months after the start of treatment being 100-97 (14-58%), 103-07 (13-45%), and 103-20 (13-92%) respectively. The mean plasma concentrations of luteinising hormone and follicle stimulating hormone fell significantly (p<0.001), and the mean plasma testosterone concentrations were significantly suppressed (p<0.001) to values seen after castration.

**Comment**

Epidemiological studies and clinical experience have shown that treatment of prostatic cancer with high doses of oestrogen increases the morbidity and mortality from cardiovascular disease. Studies seeking to establish the mechanism of this phenomenon have focused on coagulation and the fibrinolytic system. Recent studies have shown that antithrombin III concentrations are reduced during oestrogen treatment in patients with carcinoma of the prostate, and this might contribute to these patients’ increased incidence of cardiovascular complications. One quick way of obtaining information about the risk of undesirable effects of a new form of endocrine treatment is to study laboratory variables indicating or contribut-

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University Department of Therapeutics, Royal Hallamshire Hospital, Sheffield S10 2JF

R LEVIES, BSc, MRCP, research fellow
J M TONER, BSc, MRCP, research fellow
P R JACKSON, MA, MRCP, lecturer
L E RAMSAY, MB, FRCP, consultant physician and reader in clinical pharmacology and therapies

Correspondence to: Dr Ramsay.