Letters

DOI: 10.1111/dme.12321

Response to Heinzerling (Insulin allergy) and to Jacquier *et al*. (A practical, clinical approach to the assessment and management of suspected insulin allergy)

Diabet. Med. 31, 246 (2014)

I, like any other clinician who has contributed to the literature on a topic, read with interest both the article by Jacquier and colleagues and the editorial by Heinzerling on insulin allergy, but tinged with disappointment that our own observations [1] on the subject were not directly referred to, although they may have been read. We described cutaneous allergic reactions at the injection sites and, with more generalized urticaria, to some then available biosynthetic (chain recombinant bacterial and protein yeast recombinant) human insulin preparations in five patients with diabetes in 1994. The insulin manufacturers willingly disclosed the chemical contents of the non-insulin constituents of the insulin preparations suspension media. We also had available the commercial skin-prick insulin allergy test kit (Novo Nordisk Industries, Crawley, UK), which Jacquier *et al*. did not, and, by use of this and the process of elimination, concluded that these patients were not allergic to the insulin molecule itself, but to one or more of the chemical constituents of the suspension media. In three cases this was protamine, in one metacresol and in one both metacresol and phenol. Furthermore, because different insulin preparations from different manufacturers contained different chemical combinations, we were able to clinically resolve the allergy problems by using a different insulin preparation for each patient. In one case, the manufacturer supplied the short-acting insulin preparation needed in phenol rather than metacresol for some years, but, when an analogue insulin equivalent became available from them, the patient switched to this with no reaction. We did not measure anti-insulin antibodies in these patients.

The widespread use of preparations of analogues of human insulin has added another dimension to the insulin allergy story, as, theoretically at least, the altered amino acid sequences of the analogue insulin chains and biochemical additions to them provide more new potential antigens. An early review [2] noted that anti-insulin antibodies occur frequently in patients injecting bovine, porcine and biosynthetic human insulin and are of immunoglobulin G (IgG) class and variable affinities and binding capacities. Their presence in these three cases does not prove insulin allergy. Neither are they described as being specific for the analogue insulin molecule being injected. The raised serum immunoglobulin E (IgE) levels in two cases are presumably a component of the brisk allergic reaction in these two patients and not antibodies themselves. The solutions used in the intradermal insulin skin testing protocol in patients 1 and 3 were '10 insulin preparations (including recombinant human, analogue and porcine insulin preparations)', but would still contain the other constituents of these preparations, albeit now at a '1:20 dilution with normal saline'. The previously available skin test kit we used had both insulins in their suspension media and the separate chemical constituents (as we illustrated). Patient 1 did not have the disease of diabetes, had no IgE rise, and was taking aspirin and ramipril, both causes of allergic urticaria. Patient 2 had a past and family history of allergic reactions, had a reaction to her first insulin regimen and then a relapse when reverting to the short-acting insulin component of that regimen. She was desensitized using the short-acting insulin preparation for which she had proven tolerance. Patient 3 had previous drug allergy, was taking aspirin and did not react to two of the skin tested insulins, including one she was injecting.

While the publications of Jacquier *et al*. and Heinzerling add considerably to the literature on insulin allergy, and I am not being judgemental of either clinical practice or products, I suspect allergy in these cases could be explained invoking antigens other than insulin itself, and that true allergy to the native and modified insulin molecule remains a very rare phenomenon, thankfully for both patients and attending clinicians.

Funding sources

None.

Competing interests

None declared. I am now retired from clinical practice, holding full GMC Registration and Licence to Practice, and an Honorary Consultant Physician contract with the Hampshire Hospitals NHS Foundation Trust at the Royal Hampshire County Hospital, Winchester, UK. I am a member of Diabetes UK Professional Section.

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References

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2 Wiles PG. Insulin antibodies: something or nothing? *Pract Diabetes* 1988; **5**: 196.

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