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Editorial

Human Insulin: Much Ado About One Amino Acid?

G. E. Sonnenberg and M. Berger

Department of Medicine E, University of Düsseldorf, Düsseldorf, FRG

Since 1922 diabetic patients have been treated with insulin preparations extracted from the pancreas of pigs and cattle. In the early years, insulin allergy was common, but during the last five decades production techniques have become progressively more sophisticated ultimately leading to the development of 'highly purified' insulins containing less than 1 ppm proinsulin and virtually no other pancreatic peptides. When these preparations are used, especially those of porcine origin, local or systemic insulin allergy, lipodystrophy, or immunological insulin resistance occur extremely infrequently. Recently, a number of *human insulin* preparations have been produced commercially and are being promoted intensively. It had been hoped that human insulin would be entirely free of antigenicity and that its biological activity might be superior to insulins of animal origin.

Human insulin shows minor but potentially important differences from animal insulin with regard to amino acid sequences: porcine insulin differs by only one amino acid (alanine instead of threonine at the carboxy-terminal of the B chain, i.e. position B30), and beef insulin by two additional alterations of the sequence in positions A8 and A10. The amino acid sequence of commercially available human insulins is identical to pancreatic insulin in man. These preparations are produced either by a semisynthetic conversion of porcine insulin replacing alanine by threonine in an enzymatic transpeptidation process [1, 2], or by recombinant DNA technology which does not require a supply of animal pancreases. In the latter process synthetic genes for the A and B chains of human insulin are inserted into Escherichia coli, which produce separate A and B chains which are then chemically linked to form human insulin [3, 4]. An alternative would be to use a single fermentation to produce proinsulin which could then be cleaved into insulin and C-peptide. Both for the semisynthetic insulin preparation and the (biosynthetic) insulin of recombinant DNA origin, comprehensive evaluations in a variety of chemical and biological systems have confirmed their structure, identity and purity [5–7]. Biosynthetic human insulin has also been shown to be free of any potentially harmful contamination by E. coli peptides [7, 8].

Both semisynthetic and biosynthetic human insulin preparations have been studied extensively in terms of receptor binding and biological actions in vitro in animals and human subjects [9–12]. None of these studies revealed any difference between porcine and human insulins. Furthermore, human and porcine regular insulins were also indistinguishable in studies on metabolic clearance rates, plasma half-time disappearance and apparent distribution volumes [13], in glucose clamp studies [14–17], and turnover examinations on the suppressibility of hepatic glucose production and the stimulation of peripheral glucose utilization [18]. In contrast, the absorption of semisynthetic and biosynthetic regular insulins from the subcutaneous injection site into the circulation has been shown repeatedly to be slightly but significantly faster than that of corresponding porcine regular insulins in normal volunteers [19–22]. This might be explained by a somewhat greater hydrophilia of the human insulin since differences between porcine and human insulins in the hydrophilic structure of the region B28–B30 have been observed in X-ray diffraction patterns [23]. In crystallographic evaluations of their structures, regular human insulins of semisynthetic or biosynthetic origin have been indistinguishable [23]. The increased absorption of human insulin from the subcutaneous injection site might, however, not be relevant in clinical practice. For example, comparative clinical studies have shown no difference between human and porcine regular insulins in blood glucose control, insulin requirement and number of hypoglycaemic episodes in diabetic patients treated by continuous subcutaneous insulin infusion [24]. In clinical studies of (medium) long-acting insulin preparations the bioavailability of subcutaneously injected Lente-type human insulins did not differ from the corresponding porcine insulins [11]. As to protamine insulins (NPH), however, formulation of the human insulin is obviously important: biosynthetic NPH insulin shows a

more rapid onset and shorter duration of action than corresponding porcine insulins [12]. This difference is of well documented clinical relevance: higher fasting blood glucose levels have been observed in patients on human than on porcine NPH insulins [25, 26].

Considering the biological equivalence of porcine and human insulins, reports of differences in the secretion of counter-regulatory hormones after porcine and human regular-insulin-induced-hypoglycaemia were surprising; blunting of adrenaline, growth hormone and cortisol secretion following human-insulin-induced-hypoglycaemia were suggested [27, 28], although another group reported exactly the opposite for growth hormone secretion under the same conditions [29]. In a more recent study, none of these differences could be reproduced [30].

Finally, it had been hoped that therapy with human insulin preparations might prevent the formation of circulating insulin binding antibodies and hence allergic reactions. These expectations have not been fulfilled entirely. Treatment with traditional bovine insulin preparations (containing between 1000 and 10000 parts of proinsulin per million) is often associated with high levels of circulating anti-insulin antibodies, although it should be noted that a proportion of patients treated even with beef insulins do not develop antibodies, probably as a result of their genetic constitution. Since the introduction of highly purified porcine insulins, local allergy and other immunological reactions have been extremely rare. It is therefore not unexpected that all studies show human insulin to be less antigenic than the equivalent beef insulin formulation [31, 32], although subcutaneous therapy with human insulin preparations is still accompanied by the formation of some antibodies [11]. In a well controlled study the antigenicity of biosynthetic human and purified porcine insulin was significantly different after 12 months of treatment although there had been no difference at the first follow up after 6 months [33]. In general, porcine or human insulin should be preferred to beef insulin on account of the considerably higher antigenicity of the latter. In all cases of immunological insulin resistance, or allergies and local reactions against insulin, a transfer to human insulin preparations appears to be indicated – albeit it will not necessarily be successful [34]. In addition, one can justify starting insulin treatment with human insulin in young diabetic patients if circulating insulin antibodies are to be kept to a minimum. Routine transfer from highly purified porcine insulin preparations to human insulin is not indicated unless the latter is cheaper.

So far therapy with semisynthetic or biosynthetic human insulin appears safe, and free of side effects that might be attributed to their methods of production. The biological and clinical effects of human insulins show no clinically significant difference from highly purified porcine insulin preparations, and it remains to be seen whether the marginal immunological differences are of any clinical relevance. Production of human insulin cannot be regarded as a break-through in the treatment of diabetes mellitus, even though the fascinating genetic engineering and the semisynthetic method of production are remarkable steps forward in technology. The present vogue for human insulin is not matched by comparable benefits in clinical practice. The commercial versus scientific aspects of human insulin are reflected by the tide of commercially sponsored symposia, unreviewed papers and reports in books and supplements to well-known journals compared with a relatively small number of original papers on human insulin which have passed a peer review system.

The introduction of human insulin will in no way solve the multitude of problems at present involved in the treatment of insulin-dependent diabetes. On the contrary, there is a risk that the mere change to human insulin might lead some physicians and patients to the superficial and wrong impression that everything possible has been done to optimise the treatment of diabetes, whereas in reality changing a poorly controlled Type 1 diabetic patient from highly purified porcine to human insulin preparations will do nothing to improve glycaemic control. Intensified education of diabetic patients and their doctors, particularly regarding everyday metabolic self-monitoring and self-adjustment of the insulin dosage by the patients [35], re-evaluation of diet therapy [36], as well as consideration of new practices (for example insulin pump treatment), must remain the basis of the care of Type 1 diabetic patients. Human insulin for not made this difficult task any easier.

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Dr. Gabriele E. Sonnenberg
Medizinische Klinik E der Universität Düsseldorf
Moorenstraße 5
D-4000 Düsseldorf, FRG