Human and Porcine Regular Insulins Are Equally Effective in Subcutaneous Replacement Therapy

Results of a Double-Blind Crossover Study in Type I Diabetic Patients with Continuous Subcutaneous Insulin Infusion

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SUMMARY

Semisynthetic human Actrapid insulin (HAI, Novo, Copenhagen) was tested against porcine Actrapid insulin (PAI, Novo, Copenhagen) in 12 type I diabetic patients treated with continuous subcutaneous insulin infusion (CSII). In a double-blind crossover trial each patient received both types of insulin over a 3-wk period, respectively. No significant differences between HAI and PAI were observed in the following parameters: mean blood glucose levels (MBG) of 3–6 measurements per day (129 ± 5 versus 125 ± 4 mg/dl, means ± SEM), mean maximal excursions of blood glucose during the day (107 ± 6.6 versus 107 ± 6.9 mg/dl), total daily insulin requirements (sum of basal and premeal insulin doses, 45.7 ± 1.4 versus 42.7 ± 1.4 U/day), and a mean of weekly determined hemoglobin A_{1c} values (7.77 ± 0.13 versus 7.83 ± 0.14% of total hemoglobin); the frequency of mild hypoglycemic episodes was similar with the two insulins. Thus, under the controlled conditions of CSII, semisynthetic human and porcine regular insulin preparations are of identical efficacy in type I diabetic patients at near normoglycemia. DIABETES 31:600–602, July 1982.

Over the past few years, various human insulin preparations have been developed and used for investigative purposes. These human insulin preparations are produced either by chemical synthesis, semisynthetically by chemical modification of porcine insulin, or biosynthetically by recombinant DNA technology. At present, it remains unclear whether these human insulins might offer any advantages over porcine insulin preparations in the treatment of patients with diabetes mellitus. In a number of pharmacokinetic investigations, the initial absorption (and, at least in some studies, the hypoglycemic potency) of human regular insulin preparations following its subcutaneous injection in normal man was shown to be accelerated when compared with respective porcine insulin preparations.[1–3] This study was performed in order to clarify the clinical relevance of such differences under the strictly controlled conditions of a double-blind crossover trial in a highly selected, cooperative group of 12 ambulatory patients on continuous subcutaneous insulin infusion (CSII) at persistent near normoglycemia.

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METHODS

Twelve type I diabetic patients participated in the study; their mean age was 26 ± 2 yr (mean ± SEM), the duration of diabetes 12 ± 2 yr, and their basal C-peptide levels were below 0.2 ng/ml. All patients were treated by CSII using the Mill Hill Infuser, Model 1001 HM (Muirhead, England). Insulin was delivered as a continuous constant infusion rate and as premeal doses.[4] The latter was administered as a bolus infusion 15 min before each meal. Insulin was infused via a Butterfly needle into the anterior abdominal wall. The study began after a 4-wk period of CSII treatment to guarantee stabilization of metabolic control. During this 4-wk period before initiation of the experimental protocol porcine Actrapid insulin was used.

Semisynthetic human Actrapid insulin (HAI, Novo, Copenhagen, Denmark) was tested in comparison with porcine Actrapid insulin (PAI, Novo) according to a double-blind crossover protocol: in six patients treatment started with HAI and was changed to PAI after a period of 3 wk; the reverse procedure was employed in the remaining six patients. The patients were randomized by an independent statistician into three blocks of four patients each. Only after the study was finished was the randomization decoded. During the study the patients recorded the following parameters: 3–6 blood glucose measurements per day by self-monitoring (Glucosemeter, Wolf, Wuppertal, FRG), basal and premeal insulin infusion rates, hypoglycemic episodes, the carbohydrate content of their meals, and all technical problems with the pump and the catheter. For the diagnosis of hypoglycemic episodes capillary blood glucose values lower than 50 mg/dl were required. At their weekly visits to our outpatient

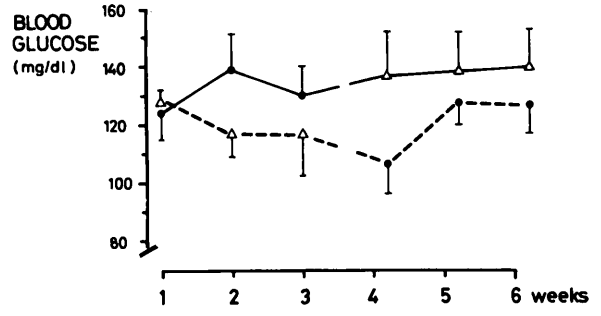

FIGURE 1. Comparison of human Actrapid insulin (HAI,△) with porcine Actrapid insulin (PAI, ●) in two groups of six type I diabetic patients treated with CSII. One group started with HAI (---) and the other one with PAI (——). Data are expressed as means ± SEM.

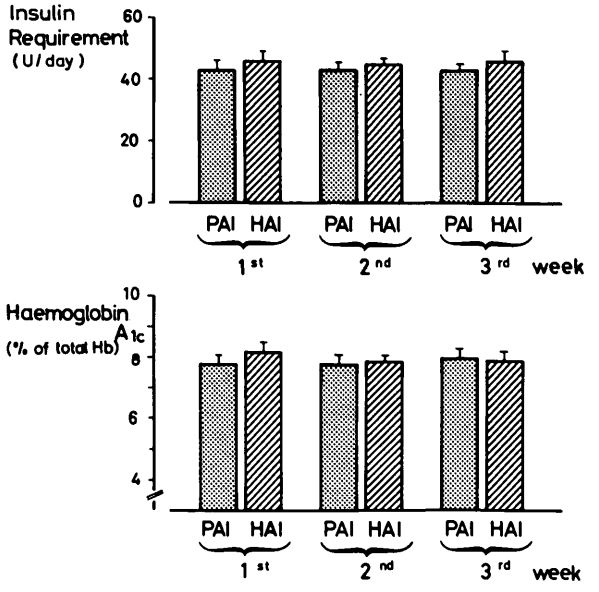

FIGURE 2. Upper graph: Insulin requirements (U/day) during treatment with porcine Actrapid insulin (PAI) and human Actrapid insulin (HAI) in 12 type I diabetic patients on CSII. Each column represents mean ± SEM of the insulin requirements per day calculated over 1 wk. Lower graph: Hemoglobin A_{1c} levels in percent of total hemoglobin during PAI and HAI treatment in the 12 patients (mean ± SEM). No significant differences between PAI and HAI treatment were observed in insulin requirements or in hemoglobin A_{1c}.

department blood samples were obtained for the determination of hemoglobin A_{1c} measured by the colorimetric procedure.[5] A questionnaire was filled out weekly to evaluate the patients' personal impression as to the effectiveness of the applied insulin.

Data were expressed as means ± SEM. Differences between HAI and PAI were calculated by Student's paired *t* test. The patients' impression as to the efficacy of HAI and PAI was evaluated by X^2 test.

RESULTS

Mean blood glucose values (MBG) during the treatment with HAI and PAI are shown in Figure 1. The MBG in the six patients who started with PAI was higher during the study period than that of the patients who started with HAI. However, the difference was not statistically significant. Also, no significant differences of MBG were observed during the treatment of HAI and PAI in each group. The MBG of all patients calculated over 3 wk was 129 ± 5 mg/dl using HAI and 125 ± 4 mg/dl using PAI. The maximal blood glucose amplitude (difference between the highest and lowest blood glucose value per day) was 107 ± 6.6 mg/dl during HAI treatment and 107 ± 6.9 mg/dl during PAI treatment. Hemoglobin A_{1c} levels also did not differ significantly between treatment of HAI and PAI (Figure 2). The hemoglobin A_{1c} levels were between 7.4% and 8.4% of total hemoglobin (normal range: 4.1–7.8%). The insulin requirements per day included the amount of the continuously administered insulin plus the premeal insulin dosages that depended on the carbohydrate content of the meals. The mean insulin requirement per day ranged between 42.5 and 46.4 U/day (Figure 2). It was larger during HAI treatment compared with PAI. However, the difference was not statistically significant. In all patients the basal insulin requirements amounted to 50–60% of the total insulin dosage per day. During HAI treatment 58 mild hypoglycemic episodes occurred and during PAI treatment 61. Thus, 4.8 ± 1.8 mild hypoglycemic episodes were observed during 3 wk of HAI treatment per patient and 5.1 ± 1.2 episodes during 3 wk of PAI treatment. Mean carbohydrate intake per day was similar during HAI and PAI treatment: about 150 g of carbohydrate per day was ingested. The body weight did not change during the study. Evaluation of the questionnaire concerning the patients' impression of the applied insulin demonstrated that 11 patients evaluated HAI as being equally or less potent than their usually applied insulin preparation and 1 patient evaluated it as being more potent. On the other hand, 6 patients estimated PAI as being equally or less potent, and 6 patients estimated PAI as being more potent than their usually applied insulin (X^2 = 3.2; df = 1; $P > 0.05$). Thus, the patients were unable to differentiate between the two types of insulin.

DISCUSSION

The results of this double-blind crossover study demonstrated that there is no difference between porcine and semisynthetic human regular insulin preparations with respect to their efficacy for subcutaneous insulin replacement therapy. With both types of insulin near normoglycemia was achieved in the 12 type I diabetic patients treated with CSII. Diurnal blood glucose excursions, insulin requirements, the frequency of mild hypoglycemic episodes, and the carbohydrate intake were essentially identical. The patients themselves were unable to differentiate between HAI and PAI.

The results of this study are in accordance with short-term and mainly uncontrolled clinical observations suggesting that purified porcine regular insulin and human insulin preparations display comparable hypoglycemic effects in type I diabetes mellitus.[6] Thus, the accelerated initial absorption of s.c. regular human insulin when compared with porcine insulin preparations in normal subjects as reported by us and other investigators[1–3] appears to be without clinical relevance. Under the controlled conditions of CSII in type I diabetic patients at near normoglycemia, human and porcine Actrapid insulin preparations were of identical efficacy. Thus, at present it seems most unlikely that the diabetes therapy of a badly controlled patient could be improved by merely changing his insulin treatment from porcine to

human insulin preparations. With respect to its hypoglycemic action and its pharmacokinetics human regular insulin does not appear to offer any advantages over purified porcine insulin preparations. Whether the s.c. treatment with human insulin preparations might be associated with a decrease of antibody formation remains to be seen.

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