Human Insulin (recombinant DNA) in the Treatment of Patients with Newly Diagnosed Insulin-dependent Diabetes Mellitus (IDDM)

NORBERT LOTZ, WERNER BACHMANN, AND HELLMUT MEHNERT

Human insulin (recombinant DNA) was administered subcutaneously to 16 patients with newly diagnosed insulin-dependent diabetes mellitus (IDDM), whereas a control group of 11 patients received highly purified pork insulin (PPI). The control group was only available for the inpatient period, while the HI-treated patients could be observed monthly afterward. For metabolic control, basal and postprandial blood glucose, plasma C-peptide, and Hb_{A1} were measured. During the outpatient period, blood glucose self-monitoring was also performed. Within 6 days of therapy, blood glucose levels were lowered to normal without any statistical differences between the HI and PPI groups. Mean insulin requirement was 35 U/day in both groups. Plasma C-peptide levels were not different at any time. In the human insulin group, Hb_{A1} values were continuously lowered from the initial 13% to the normal range within 2–3 mo and remained normal after 6 mo of therapy. No allergic reaction and no other side effects could be seen. The results suggest that in the first period of treatment, the metabolic situation of patients with IDDM could be well controlled by human insulin as well as by PPI. Human insulin has been proven to be an effective and safe insulin. DIABETES CARE 5 (SUPPL. 2): 149–151, 1982.

As far as the immunologic aspects are concerned, human insulin (recombinant DNA) should be advantageous in the treatment of patients with newly diagnosed IDDM. This advantage counts only if metabolic efficiency is comparable with that of animal insulin preparations. Up to now, a lot of in vitro (for review see ref. 1) and short-term in vivo[2] studies have been performed in human beings, ensuring that human insulin is an effective and safe insulin preparation.

In our study, 16 patients with newly diagnosed IDDM were treated with human insulin and compared with 11 patients treated with purified porcine insulin (PPI) with regard to each insulin's effect on blood sugar, C-peptide, and insulin requirement.

SUBJECTS AND METHODS

Twenty-seven patients with newly diagnosed IDDM, aged 14–52 yr, were studied. Aside from diabetes mellitus, none of the patients had any acute or chronic disease. In a random regimen, 16 patients (9 men and 7 women) were treated with human insulin and 11 (6 men and 5 women) received pork insulin. No patient was ever treated with insulin before. All patients were informed according to the rules of the Geneva,

TABLE 1
Clinical and biochemical data of patients with newly diagnosed IDDM ($\bar{x}$ ± SEM)

	Age (yr)	Sex	% Ideal body weight	Cholesterol (mg/dl)	Triglycerides (mg/dl)
Treatment with human insulin (N = 16)	31 (15–52)	9M, 7W	106 ± 5	231 ± 13	177 ± 33
Treatment with pork insulin (N = 11)	26 (14–34)	6M, 5W	100 ± 4	235 ± 29	122 ± 23

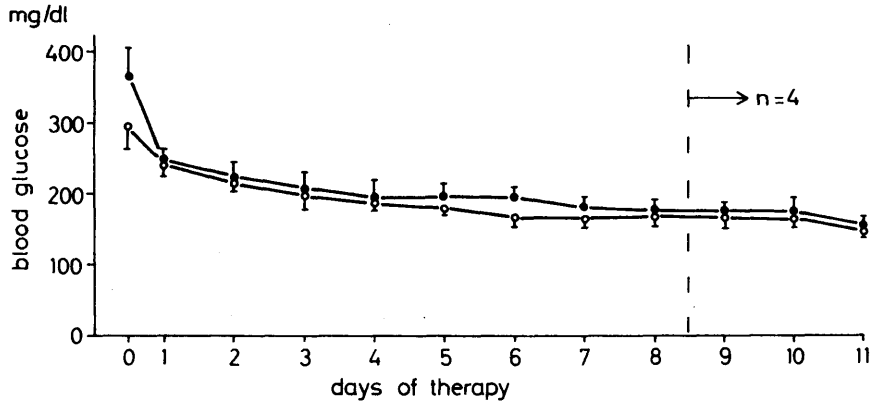

FIG. 1. Mean plasma glucose ($\bar{x} \pm$ SEM) in patients with newly diagnosed IDDM during the initial period of insulin therapy with human insulin ($N = 16$; ●——●) or highly purified pork insulin ($N = 11$, ○——○).

Helsinki, and Oslo declarations of the nature of the study and gave their consent to participate.[3]

Capillary blood for the determination of blood glucose was taken basally and 1 h postprandially at 9 a.m. and 1 p.m. Venous blood samples were taken from the vena mediana cubiti for the determination of plasma C-peptide,[4] cholesterol, and triglycerides before starting, and on days 1 and 5 after insulin treatment. Hb_{A1} was measured before and once a month after the beginning of insulin therapy. Whereas the human insulin group was observed once a month after being discharged, the pork insulin group was only available for the inpatient period. During the outpatient period, the human insulin group performed blood glucose self control 3 days a week by the Ames dextrometer. Statistical calculations were done by the Student t test.

RESULTS AND DISCUSSION

In our study, human insulin was compared with pork insulin in two groups of IDDM patients. No significant differences in basal clinical and biochemical data could be observed between the groups (Table 1). All patients had a short history of diabetes with weight loss, polyuria, and polydipsia. In each patient the initial blood glucose was above 250 mg/dl, with pronounced glucosuria and ketonuria.

As shown in Figure 1, initial mean blood glucose was lowered from 365 ± 45 mg/dl ($\bar{x} \pm$ SEM) to 192 ± 12 mg/dl in the human insulin group and from 294 ± 32 mg/dl to 168 ± 13 mg/dl in the pork insulin group within 6 days of insulin therapy. The four patients in each group who could not be dismissed within 8 days revealed a higher need for insulin for good metabolic control, as shown in Figure 1.

During hospitalization, there was no significant difference in total insulin requirement between the two groups, suggesting an identical metabolic efficiency of both insulin preparations (Figure 2). This is in accordance with investigations of Raptis and Massi-Benedetti.[5,6]

As a consequence of good metabolic efficiency, human insulin as well as pork insulin led to a diminution of basal C-peptide from 0.21 ± 0.06 nmol/L to 0.10 ± 0.05 nmol/L and from 0.30 ± 0.1 nmol/L to 0.17 ± 0.03 nmol/L, respectively. Whereas no significant rise of postprandial compared with basal C-peptide levels could be measured on days 0 and 1, this was valid after improvement of metabolic control ($P < 0.05$) on day 5 of treatment. The failure of physiologic regulation of C-peptide on day 0 could be due to a maximal stimulation of beta-cell secretion by constantly high blood glucose levels and on day 1 to a possible hyperinsulinism (Figure 3).

Monthly metabolic control of the human insulin (rDNA)-

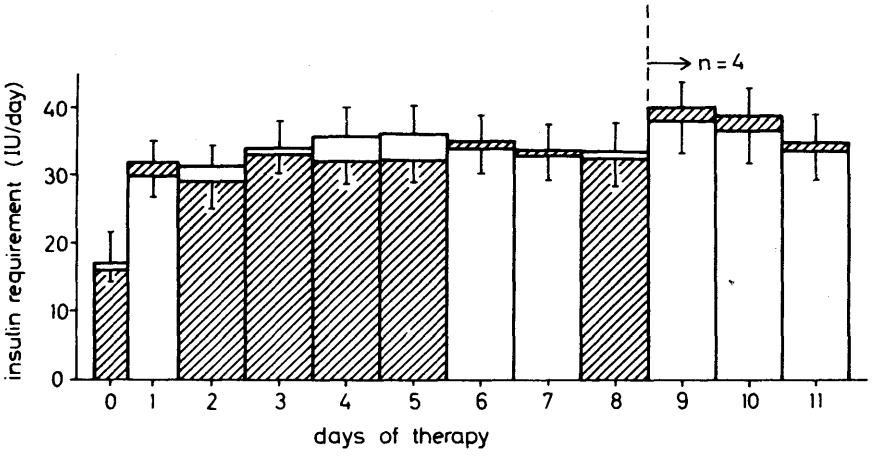

FIG. 2. Mean insulin requirement ($\bar{x} \pm$ SEM) in patients with newly diagnosed IDDM during the initial period of insulin therapy with human insulin ($N = 16$; ▨) or highly purified pork insulin ($N = 11$; □).

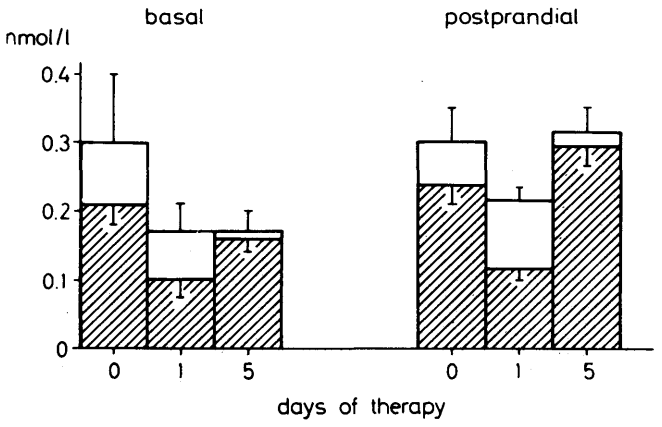

FIG. 3. Mean basal and postprandial C-peptide levels ($\bar{x} \pm SEM$) in patients with newly diagnosed IDDM treated with human insulin ($N = 16$; ▨) or highly purified pork insulin ($N = 11$; □) before (0) and on days 1 and 5 after insulin therapy.

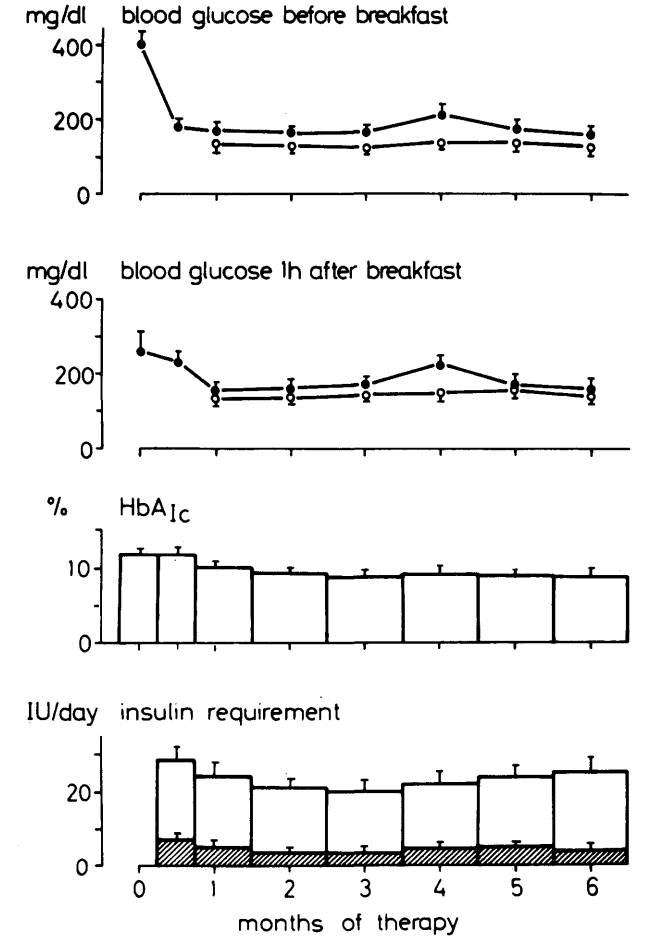

FIG. 4. Mean basal and postprandial blood glucose (●——● laboratory and ○——○ self monitoring), mean Hb_{A1} values, and mean insulin requirement (total insulin □; regular insulin ▨) in 16 patients with newly diagnosed IDDM on human insulin during the outpatient period ($\bar{x} \pm SEM$).

treated patients showed values of basal blood glucose up to 211 ± 24 mg/dl (Figure 4). However, postprandial blood glucose levels were within the normal range, corresponding to normal Hb_{A1} values (<9%). Since blood glucose values determined by home glucose monitoring were constantly lower (about 21%) than the laboratory measurements, these enhanced values are probably due to a delay of the morning insulin injection on control days and to the method of self control used. As to our experience, the blood glucose measurements with Ames dextrometer are generally lower, about 30–50 mg/dl, than by the hexokinase method.

Mean insulin requirement at the end of the first month was 24 ± 3 U/day. In seven human insulin–treated patients, a remission phase could be observed with a daily insulin dosage of less than 20 U. Since the nadir of total insulin requirement after 3–4 mo with 21 U/day, a slow increase in insulin dosage up to 25 ± 4 U/day occurred up until now, after 6 mo of therapy.

Insulin was given either as pure NPH preparation or as an individual mixture of NPH/Regular. Only three patients received NPH insulin; two of them as a single insulin injection once a day; 13 patients received a mixture of NPH and regular insulin in two injections a day. The mean portion of regular insulin was 20% of the total, but there was a wide range of variation from 15 to 50%. No side effects of human insulin were seen, and above all, no allergic reaction occurred.

The metabolic situation of patients with IDDM could be controlled very well using human insulin with nearly normal blood glucose concentrations and normalization of Hb_{A1}. There was no difference between human insulin and commercial highly purified pork insulin preparations. Therefore, human insulin (rDNA) can be considered as an effective and safe insulin for subcutaneous administration in IDDM.

From the Schwabing City Hospital, Kölner Platz 1, 8000 Munich 40, West Germany.

Address reprint requests to Norbert Lotz, Städtisches Krankenhaus München-Schwabing, III. Medizinische Abteilung, Kölner Platz 1, 8000 München 40, West Germany.

REFERENCES

[1] De Meyts, P., Halban, P., and Hepp, K. D.: In vitro studies on biosynthetic human insulin: an overview. Diabetes Care 4: 144–46, 1981.

[2] Skyler, J. S., and Raptis, S. (Eds.): Symposium on biosynthetic human insulin. Diabetes Care 4: 155–62, 163–67, 170–74, 175–79, 180–82, 183–88, 189–92, 193–95, 205–208, 1981.

[3] World Medical Association: Geneva, Helsinki, Sidney and Oslo Declarations. Br. Med. J. 1: 678, 1973.

[4] Hedig, L. G.: Radioimmunological determination of human C-peptide in serum. Diabetologia 11: 541–48, 1975.

[5] Raptis, S., Karaiskos, C., Enzmann, F., Hatzidakis, D., Zoupas, C., Souvatzoglou, A., Diamantopoulos, E., and Moulopoulos, S.: Biologic activities of biosynthetic human insulin in healthy volunteers and insulin-dependent diabetic patients monitored by the artificial endocrine pancreas. Diabetes Care 4: 155–62, 1981.

[6] Massi-Benedetti, M., Burrin, J. M., Capaldo, B., and Alberti, K. G. M. M.: A comparative study of the activity of biosynthetic human insulin and pork insulin using the glucose clamp technique in normal subjects. Diabetes Care 4: 163–67, 1981.