Comparison of the Activity Profiles of Two Fixed Combinations of Regular/NPH Human Insulin (recombinant DNA) of Different Compositions with a Fixed Regular/NPH Porcine Insulin Combination (PPI) in Insulin-dependent Diabetic Individuals

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In a randomized double-blind crossover study, 10 insulin-dependent diabetic individuals were treated with a commercial brand of neutral, highly purified porcine insulin (PPI) with 30% regular and 70% NPH fractions (Mixtard, Nordisk, Denmark), and with human insulins (recombinant DNA) with 20% regular and 80% NPH fractions, and with 30% regular and 70% NPH fractions. Each of the preparations was given for 4 consecutive days. The human insulin combination with the 20% regular and 80% NPH components showed a similar activity profile as the PPI 30/70 combination. In contrast, the human insulin combination with the 30% regular and 70% NPH fractions produced substantially lower blood sugar concentrations with the associated risk of hypoglycemia. DIABETES CARE 5 (SUPPL. 2): 57–59, 1982.

The synthesis of the insulin A and B chains by recombinant DNA methods using *E. coli* fermentations was reported recently by Goeddel et al.[1] In vitro studies and studies carried out in healthy test persons and in insulin-dependent diabetic individuals showed that the biological efficacy of human insulin (recombinant DNA) is practically comparable with that of porcine insulin (PPI).[2,3-5] If applied subcutaneously, however, human insulin seems to be absorbed more rapidly than porcine insulin.[6]

The insulin preparations available up to now were neutral regular insulin and neutral protamine Hagedorn insulin (NPH); however, galenic principles allowed the regular and depot components to be freely combined. A fixed combination would be more desirable, however, as the majority of diabetic individuals cannot reasonably be expected to mix their own insulin preparations.

We therefore investigated two fixed combinations of human insulin with different regular and depot concentrations to ascertain the quality of blood sugar adjustment in insulin-dependent diabetic individuals and compared the results with a commercial, highly purified porcine insulin preparation.

PATIENTS AND METHODS

Patients. Ten volunteer, insulin-dependent diabetic persons, who had been stabilized under a commercial brand of neutral, highly purified porcine insulin, were included in the study. The youngest patient was 21 and the oldest 80 yr old; the average age was 50 ± 19 yr. Three of the patients were women and the remaining 7 were men. All patients had been insulin-dependent for at least 6 mo; the mean duration of diabetes was 10 ± 4.7 yr (2–18 yr).

All test subjects were fully enlightened as to the nature and the purpose of the study, and after a few days of consideration all gave their written consent to voluntary participation in the study.

Furthermore, after describing our projected test setup, we received the written approval of the Ethics Commission of our hospital before the study began.

Insulins. We were supplied with human insulin in two different preparations from Eli Lilly (Indianapolis, Indiana). The first preparation (depot A) contained 30% neutral regular and 70% neutral protamine Hagedorn insulin (NPH); this ratio was 20% to 80% in the second preparation (depot B). A commercial brand of neutral porcine insulin with 30% regular and 70% NPH components was used for reference purposes (Mixtard).

Study design. The study was performed as a double-blind crossover study under steady-state conditions. The manufacturer did not inform us of the respective compositions of depot A and depot B until the entire study had been completed.

The patients, who had been adequately stabilized under Mixtard insulin, were observed for 4 days during which time they received a constant carbohydrate and calorie supply and an unchanged insulin dose. On the fourth day, blood sugar was intensively monitored with 24 individual blood sugar

TABLE 1
Observed incidence of hypoglycemia under human insulin-depot A, human insulin-depot B, and Mixtard insulin

Blood sugar (mg/dl)	Mixtard I	Depot A	Depot B	Mixtard II
< 80	12	31	17	14
< 60	2	8	5	4
< 50	0	3	1	0

TABLE 2
MBG and MAGE under Mixtard I and II and depot A and depot B human insulin

	MBG (mg/dl)	MAGE (mg/dl)
Mixtard I	150 ± 26	128 ± 29
Depot A	125 ± 33	118 ± 44
Depot B	139 ± 26	115 ± 33
Mixtard II	147 ± 27	128 ± 42

determinations/24 h. Thereafter, five of the patients were changed to an equivalent dosage of depot A and five patients to depot B. After a further 4-day period, an intensive 24-h profile was prepared once more, the insulin preparations crossed over, and 4 days later yet another intensive 24-h profile prepared. Subsequently, all patients received Mixtard insulin again, and after 4 days underwent an examination of blood sugar homeostasis. The food supply and insulin dosage remained unchanged in all patients throughout the 16-day test period.

RESULTS

The insulin preparations depot A and depot B were tolerated well. No complications were observed. The injection sites, which were examined daily, revealed no abnormalities. Blood sugar reductions under depot A and depot B insulin were at least as pronounced as under Mixtard insulin, and in part—especially under depot A insulin—considerably more so. Hypoglycemia with values of less than 50 mg/dl was not observed during the two Mixtard periods. During administration of depot A insulin, blood sugar concentrations of less than 50 mg/dl were observed three times; the lowest blood sugar value measured was 40 mg/dl. Hypoglycemia was determined only once under depot B insulin at 43 mg/dl.

Table 1 shows the incidence of hypoglycemia during administration of the different insulin types.

If the mean blood sugar values recorded at the various times throughout the day are compared with one another, it is noticeable that the blood sugar level under depot A insulin is distinctly lower, revealing its lowest (sometimes hypoglycemic) concentrations in the late morning and early afternoon. Depot B insulin, on the contrary, revealed a more balanced profile by arresting food-induced hyperglycemia with reduced risk of hypoglycemia. Its overall behavior approaches that of Mixtard insulin (Figure 1).

The mean blood sugar concentrations (MBG) recorded on the measuring day and the maximum blood sugar amplitudes (MAGE) are summarized in Table 2. It is noticeable here that depot A insulin with 125 ± 33 mg/dl reveals its lowest MBG at an MAGE of 118 ± 44 mg/dl. With depot B insulin, the MBG value was 139 ± 26 mg/dl with an MAGE value of 115 ± 30 mg/dl. During administration of Mixtard insulin, the MBG value was 150 ± 26 mg/dl and 147 ± 27 mg/dl for MAGE values of 128 ± 29 mg/dl and 128 ± 42 mg/dl, respectively.

DISCUSSION

Combination insulins have proven their value in the treatment of insulin-dependent diabetic individuals. One insulin type that has particularly stood out in West Germany in recent years is a highly purified neutral porcine insulin with 30% regular and 70% NPH fractions (Mixtard insulin). It is

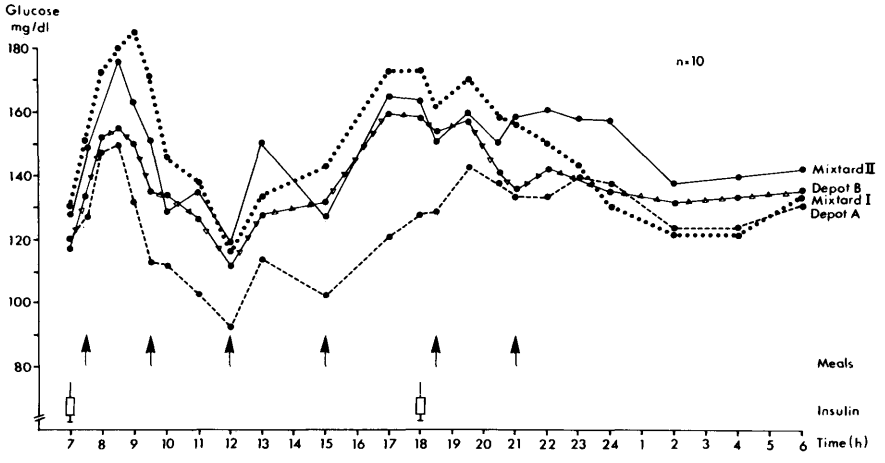

FIG. 1. Blood glucose pattern by 10 insulin-dependent diabetic individuals under Mixtard I and II and depot A and depot B human insulin (recombinant DNA).

therefore meaningful to compare new insulin preparations with the activity profile of Mixtard insulin.

A fixed regular/NPH combination of human insulin has so far not been available, although it is indispensable in day-to-day practice.

The 20/80 (depot B) and 30/70 (depot A) combinations that we examined were characterized by good blood sugar-reducing properties. It was seen that the 30% regular and 70% NPH combination (depot A) of human insulin possesses more pronounced hypoglycemic properties than the same combination of highly purified porcine insulin. This confirms findings by Bottermann[6] that human insulin administered subcutaneously is absorbed more rapidly than porcine insulin. The activity profile of a combination consisting of 20% regular and 80% NPH human insulin is very similar to that of Mixtard insulin, whereas a larger fraction of regular insulin distinctly increases the risk of hypoglycemia.

In our investigations it was conspicuous that hypoglycemic reactions under human insulin were not experienced subjectively in the great majority of cases. Other authors have already reported similar findings[5,7] whereby smaller concentrations of the counterregulatory hormones were found following hypoglycemia induced with human insulin.[7] This may suggest the possibility of stricter metabolic control through the use of human insulin.

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