A Comparison of Premixed Insulin Preparations in Elderly Patients

Efficacy of 70/30 and 50/50 human insulin mixtures

ROBERT BRODOWS, MD
RUTH CHESSOR, LPN

OBJECTIVE — To compare the postprandial hyperglycemic response to a standard breakfast of two premixed humulin insulin mixtures, 50/50 (50% NPH human insulin and 50% regular human insulin) and 70/30 (70% NPH human insulin and 30% regular human insulin) in elderly non-insulin-dependent diabetes mellitus (NIDDM) patients.

RESEARCH DESIGN AND METHODS — On two mornings, each patient (n = 20) consumed a standard breakfast after a single dose of 50/50 or 70/30 insulin (0.3 U/kg) was administered in a randomized crossover fashion. Plasma glucose and serum free insulin concentrations were measured before and for 4 h after insulin administration.

RESULTS — Plasma glucose reached a peak at 60 min and a nadir at 240 min for both types of insulin. No differences in maximum and minimum glucose concentrations, time to maximum and minimum glucose concentrations, or areas under the curve were noted. Free insulin levels did not differ significantly.

CONCLUSIONS — These results suggest that small changes in the composition of premixed insulin mixtures in NIDDM patients may not result in improved postprandial glycemic control.

Patients with non-insulin-dependent diabetes mellitus (NIDDM) who require insulin are often elderly and may have impaired motor skills or diminished vision or be in social situations that make it difficult to accurately draw up mixtures of insulin (1,2). Currently, two premixed insulin preparations are available in the U.S. with ratios of NPH and regular human insulin of either 70/30 or 50/50. This should allow for more convenience and flexibility for elderly NIDDM patients and health care providers in achieving adequate glycemic control. Studies on the pharmacokinetics and glucodynamics of the 50/50 mixture in normal subjects suggest that it should useful for patients requiring more immediate postprandial glucose control (3). However, no direct comparison of these two preparations has been made in NIDDM subjects. The present study compares the postprandial response to a standard breakfast achieved by a fixed dose of 70/30 and 50/50 insulin in an elderly group of NIDDM subjects.

RESEARCH DESIGN AND METHODS

— Twenty patients with NIDDM participated in this study. All patients were currently on a regimen including both NPH and regular insulin. To be eligible, the patients had to have basal C-peptide values >0.07 nmol/l and body mass index <38. Table 1 lists the clinical characteristics of the group. All subjects were studied in the postabsorptive state at 0730 on two separate occasions that were at least 1 week apart. Intermediate-acting insulin was discontinued, and subjects were given three or four injections of short-acting insulin for 24 h before each experiment. Thirty minutes before breakfast, subjects were randomized to receive either Humulin 70/30 or Humulin 50/50 in a dosage of 0.33 U/kg body wt in the subcutaneous tissue of the anterior abdominal wall. A standard breakfast consisting of 340 kcal with 50% carbohydrates, 20% fat, and 30% protein was consumed over 15 min. Blood samples were obtained before and for 4 h after insulin administration for measurement of glucose and free insulin. During the testing, subjects remained seated during the entire study.

Determinations and statistical analysis

Plasma glucose was determined with a Kodak Ectachem d60 analyzer. Free insulin was measured in the laboratory of Dr. S. Edwin Fineberg, Indianapolis, IN. Statistical significance was tested by repeated-measures one way analysis of vari-

Address correspondence and reprint requests to Robert Brodows, M.D., 393 Wallace Road, Nashville, TN 37211.

Received for publication 7 December 1994 and accepted in revised form 26 January 1995.

AUC, area under the curve; NIDDM, non-insulin-dependent diabetes mellitus.

Table 1—*Baseline characteristics of study population*

Age (years)	66.9 ± 6.9
M/F	11/9
Body mass index	28.7 ± 4.7
Duration (years)	10.5 ± 5.9
Fasting C-peptide (nmol/l)	0.93 ± 0.60
Glycohemoglobin (%)	8.7 ± 0.87
Daily insulin dose (U)	55.3 ± 24.0

Data are means ± SD.

ance followed by Scheffe's *F* test or, when appropriate, Student's paired two-tailed *t* test. Area under the curve (AUC) was calculated by the trapezoidal method.

RESULTS — The plasma glucose responses to both 70/30 and 50/50 insulin after the mixed meal are shown in Fig 1. Preprandial plasma glucose was almost identical for both experiments (11.6 ± 2.2 vs. 11.1 ± 2.7 mmol/l). Plasma glucose reached a peak at 60 min and a nadir at 240 min for both types of insulin. Various glucokinetic parameters were calculated from the glucose data, including maximum and minimum glucose concentrations (C_{max}, C_{min}), time to maximum and minimum glucose concentrations (T_{max}, T_{min}), and AUCs from 0 to 240 min. There were no statistical differences between treatments. Furthermore, there was no correlation between fasting plasma glucose and any of the glucokinetic parameters. Plasma free immunoreactive insulin concentrations tended to peak earlier with 50/50 insulin, but the AUCs and the maximum glucose concentrations were almost identical for both types of insulin (Fig. 1).

CONCLUSIONS — In the U.S., clinicians currently have the option of two premixed human insulin preparations, 70/30 and 50/50. In Europe, five preparations are available, and it is possible that there will be additional mixtures for use in the U.S. in the near future. There is no doubt that premixed insulin regimens improve the accuracy of insulin dosing (4). Furthermore, patients find premixed insulin easier to use and more convenient than self-mixing (5). However, whether these premixed preparations in fact allow certain NIDDM patients to better control their diabetes remains to be proven.

In spite of differences found in healthy subjects given 70/30 and 50/50 during euglycemic clamp studies (3), our findings fail to document any benefit of one premixed preparation over the other in NIDDM patients who regularly take insulin. The dietary intake, site of injection, and timing of injection was carefully controlled. Premeal plasma glucose was similar at the start of each experiment. The glycemic response was essentially the same despite an average increase of 6 U of regular insulin (range 4.6–8.6 U) when the 50/50 preparation was administered. These results agree with the impression of others that fine-tuning protocols of intermediate- and fast-acting insulin may be futile (6–8). Recently, Lindstrom et al. (8) reported similar overall glucose control with two- and four-dose insulin regimens in patients with NIDDM treated with insulin after failure of oral agents.

Several mechanisms may have contributed to the present findings. Regular insulin is absorbed more quickly than NPH (9,10); thus, one would expect 50/50 insulin to result in greater free insulin concentrations. This study's inability to detect such differences might reflect the well-documented erratic absorption of subcutaneous insulin (7). In addition, differences in endogenous insulin production may also have masked the glycemic response, since all patients were producing some endogenous insulin. Differences in insulin mixtures might be more apparent when insulin deficiency is the predominant cause of hyperglycemia. Unfortunately, the C-peptide response was not measured after the test meals, so the contribution of endogenous insulin during these experiments is unknown. Finally, the degree of insulin resistance in our subjects may have made the small increase in the amount of regular insulin administered in the 50/50 experiment less effective.

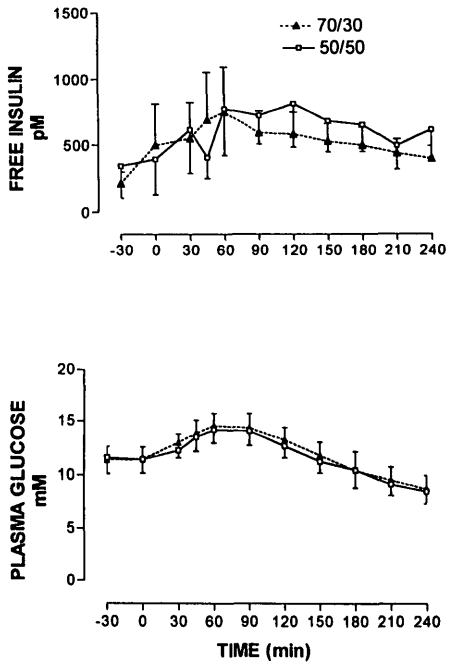

Figure 1—*Plasma glucose and free insulin levels after ingestion of standard meal and administration of the 50/50 or the 70/30 mixture. Means ± SE.*

Some clinicians might be hesitant to use 50/50 insulin for fear of creating hypoglycemia in the immediate postprandial period. However, only 1 of the 20 subjects in this study actually became hypoglycemic enough to warrant treatment in the 3rd h after insulin administration. Of note is the fact that this occurred with both premixed preparations. Thus, it appears that hypoglycemia may not be a significant worry when doses of 0.33 U/kg are used in elderly NIDDM patients with fasting plasma glucose in the 200 mg/dl range. No correlation existed between fasting plasma glucose and the glycemic response to breakfast; therefore, patients with lower fasting glucose were not necessarily at increased risk of hypoglycemia. However, the fasting glucose level was never <148 mg/dl in this study.

In conclusion, based on the present study, it does not seem worthwhile to consider switching to a premixed preparation of 50/50 insulin in elderly NIDDM patients already taking a 70/30

mixture in an attempt to improve postprandial glycemic control. Because our findings were limited to 4-h testings in a minimal activity setting, a crossover study of longer duration would be helpful to further assess the role of these preparations in management of NIDDM in elderly patients.

Acknowledgments— This work was supported by a grant from Eli Lilly, Indianapolis, IN.

References

1. Puxty JAH, Hunter DH, Burr WA: Accuracy of insulin injection in elderly patients. *Br Med J* 287:1762, 1983
2. Coscelli C, Calabrese G, Fedele D, Pisu E, Calderini C: Use of premixed insulin among the elderly. *Diabetes Care* 15: 1628–1630, 1992
3. Woodworth JR, Howey D, Bowsher RR, Brunelle RL, Rowe HM: Comparative pharmacokinetics and glucodynamics of two human insulin mixtures. *Diabetes Care* 17:366–371, 1994
4. Bell DSH, Clements RS, Perentesis G, Roddam R, Wagenknecht L: Dosage accuracy of self-mixed vs premixed insulin. *Arch Int Med* 151:2265–2269, 1991
5. Bell D, Bode B, Clements RS, Jerron J, Hollander PA: Premixed vs. self-mixed insulin in the treatment of type II diabetes mellitus: a randomized trial. *Today's Ther Trends* 9:63–73, 1991
6. Lauritzen T, Pramming S, Gake EAM, Deckert T, Binder C: Absorption of isophane (NPH) insulin and its clinical implications. *Br Med J* 285:159–162, 1982
7. Galloway JA, Spardlin CT, Nelson RS, Wentworth SM, Davidson JA, Swarner JL: Factors influencing the absorption, serum insulin concentrations, and blood glucose responses after injections of regular insulin and various insulin mixtures. *Diabetes Care* 4:366–376, 1981
8. Linstrom TH, Arnqvist HJ, von Schenck HH: Effect of conventional and intensified insulin therapy on free-insulin profiles and glycemic control in NIDDM. *Diabetes Care* 15:27–34, 1992
9. Berger M, Cuppers HJ, Hegner H, Jorgens V, Berchthold P: Absorption kinetics and biological effects of subcutaneously injected insulin preparations. *Diabetes Care* 5:77–91, 1982
10. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–199, 1984