Comparison of Bedtime NPH or Preprandial Regular Insulin Combined With Glibenclamide in Secondary Sulfonylurea Failure

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OBJECTIVE — To compare the effect of bedtime NPH insulin or preprandial regular insulin combined with glibenclamide on metabolic control in non-insulin-dependent diabetes mellitus (NIDDM) patients with secondary failure to sulfonylurea therapy.

RESEARCH DESIGN AND METHODS — Eighty NIDDM patients were randomized to treatment with either three preprandial doses of regular insulin (daytime insulinization, group D) or a bedtime dose of NPH insulin (nocturnal insulinization, group N), both regimens being combined with 10.5 mg of glibenclamide. Metabolic profiles were obtained at 0, 6, and 16 weeks.

RESULTS — Glycemic control had improved significantly in both groups after 4 months. Fasting blood glucose was significantly lower compared with baseline in both groups. The mean change ± SD in group D was −2.8 ± 3.5 mmol/l and in group N −6.4 ± 3.0 mmol/l, the reduction being more pronounced in group N compared with group D ($P < 0.0001$). HbA_{1c} was lowered similarly, from 9.2 ± 1.4 to 7.1 ± 1.2% in group D ($P < 0.0001$) and from 9.1 ± 1.1 to 7.5 ± 1.5% in group N ($P < 0.0001$). The total daily insulin doses were similar, 29 ± 11 U in group D and 26 ± 9 U in group N, and the circulating insulin levels during daytime were higher in group D than in group N. Total serum cholesterol and triglycerides were similarly and significantly lowered compared with baseline in both groups. Weight gain was more pronounced in group D (3.4 ± 0.3 kg) than in group N (1.9 ± 1.9 kg; D vs. N, $P < 0.002$), and the change was inversely correlated with the initial weight but not with the improvement in HbA_{1c}.

CONCLUSIONS — The two insulin regimens exert similar effects on glucose metabolism and serum lipids in NIDDM patients on combination therapy. Weight gain is more pronounced in patients given insulin during the daytime when preprandial doses of short-acting insulin are used.

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BMI, body mass index; FBG, fasting blood glucose; NIDDM, non-insulin-dependent diabetes mellitus.

Non-insulin-dependent diabetes mellitus (NIDDM) may be looked upon as a progressive disease where glycemic control gradually deteriorates with time. Thus, despite diet, exercise, and oral sulfonylurea treatment, 5–10% of these patients annually display inadequate metabolic control, i.e., develop secondary failure to sulfonylurea (1). Several different insulin regimens have been tried in the treatment of these patients, including intensive conventional insulin therapy (2–4). During recent years, the combination of insulin and sulfonylurea has come into focus and a number of studies have documented that this treatment is more effective in improving metabolic control (2,5,6). In a meta-analysis of 17 studies, the investigator concluded that combined sulfonylurea-insulin therapy leads to modest improvement in glycemic control compared with insulin therapy alone and that lower insulin doses may be used in combination therapy to achieve similar control (7). Only a few studies (2,5,6) have addressed the question of which insulin regimen is optimal in combination with sulfonylurea treatment, and no consensus concerning this issue is presently at hand. In the present study, we compared bedtime NPH insulin, giving mainly nocturnal insulinization (group N), with three preprandial doses of regular insulin, giving mainly daytime insulinization (group D), in combination with a maximal dose of oral glibenclamide therapy in NIDDM patients with secondary failure to sulfonylurea.

RESEARCH DESIGN AND METHODS

— Patients referred to the participating clinics because of secondary failure to sulfonylurea were included if the following criteria were met: *1*) age 40–80 years with 2) clinical diagnosis of NIDDM and 3) current body mass index (BMI) of 22–30 kg/m^2 and 4) fasting blood glucose (FBG) >10 mmol/l at least two times during the last 3 months despite 5) maximal daily dose of glibenclamide (≥10.5 mg) or glipizide (≥15

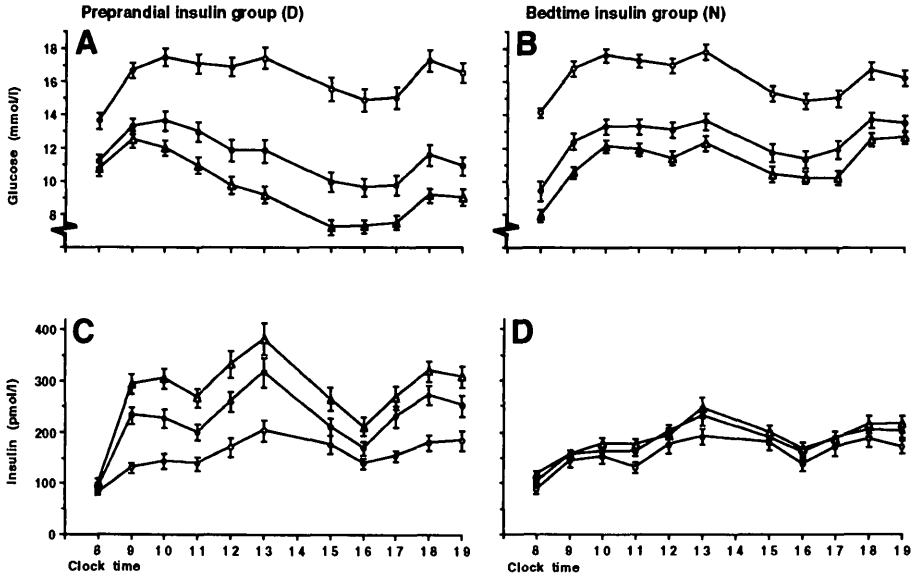

Figure 1—*Profile 1 (○), profile 2 (●), and profile 3 (△) of blood glucose (A,B) and total plasma insulin (C,D). Patients treated with preprandial regular insulin three times daily (group D) shown on left panels; patients treated with bedtime NPH insulin (group N) shown on right panels.*

mg) for at least 3 months. Criteria for exclusion were renal disease, liver dysfunction, contemporaneous acute disease, and psychiatric disturbances. The study was approved by the local ethics committee.

Eighty patients (56 men and 24 women), mean age 59 (43–76) years, were included and randomized to group D, preprandial insulin (n = 41), or group N, bedtime insulin (n = 39). The known diabetes duration was 9 ± 5 years, body weight 78.4 ± 9.8 kg, BMI 26.2 ± 2.3 kg/m^2, FBG 13.7 ± 2.2 mmol/l, HbA_{1c} 9.1 ± 1.3%, fasting C-peptide 0.90 ± 0.25 nmol/l, and fasting plasma insulin 85 ± 43 pmol/l. There were no significant differences between the two groups in these parameters.

During a run-in period of 2 weeks, the patients were treated with 10.5 mg/day glibenclamide, after which they were admitted to the clinic for laboratory tests and initiation of insulin therapy. Fasting blood samples were collected for serum lipids, C-peptide, glucose, insulin, and HbA_{1c}, and thereafter, blood samples were collected hourly between 0800 and 1900, for analyses of glucose and insulin. C-peptide was analyzed at 0800, 0900, and 1000.

Randomization to either preprandial regular insulin, given before breakfast, lunch, and dinner, or bedtime NPH insulin was made during day 1, and the insulin treatment was started the same evening (in group N) or the following morning (in group D). During the first 6 weeks of insulin treatment, the patients received a fixed insulin dose of 0.25 U · kg body wt^{-1} · day^{-1}. In group D, the dose was divided and given as regular insulin (Isuhuman Rapid, Hoechst AG) with one-third of the daily dose before each meal. In group N, the insulin dose was administered at bedtime as NPH insulin (Isuhuman Basal, Hoechst AG).

All patients were asked to perform self-monitoring of blood glucose and were instructed to bring a blood glucose profile to all subsequent visits performed the day prior to the visit. No regular visits were scheduled during the first 6 weeks, and at the end of this period the patients were admitted to the hospital for 1 day to obtain new fasting values and a second profile. Between weeks 7 and 16 the patients were seen at three visits at which the insulin dose was adjusted with the aim of reaching the targets on glucose control given by the European NIDDM Policy Group, i.e., FBG <6.7 mmol/l and postprandial blood glucose values <8.9 mmol/l (8). No additional increase of the insulin dose was allowed during the last month of the study, and the third profile was obtained after 16 weeks.

Of the 80 patients who began the study, 76 completed the protocol. Four patients discontinued for various reasons: one was unwilling to continue, one was excluded because he needed cortisone medication, and two patients had recurrent, but not severe, hypoglycemia.

Analytical methods

Blood glucose was measured with the hexokinase glucose-6-phosphate dehydrogenase reaction (Paramax analyzer, Baxter, Sacramento, CA). HbA_{1c} was determined with high-performance liquid chromatography (Pharmacia, Uppsala, Sweden; reference range <5.3% in nondiabetic control subjects). Radioimmunoassay methods were used for determination of serum C-peptide (RIA-gnost hC-peptide, Hoechst, Germany) and plasma insulin (Pharmacia). Serum lipids were determined with enzymatic methods in a routine autoanalyzer (Paramax analyzer, Baxter).

All data are expressed as means ± SD. Statistical analyses were performed using the appropriate Student's two-tailed t test or by simple regression analysis.

RESULTS— The two groups exhibited similar profiles of blood glucose and total plasma insulin at the start (Fig.1), and the means of all blood glucose values obtained during the first profile were close to identical in group D and group N (Table 1).

During the first 6 weeks, the mean ± SD insulin dose given was 18 ± 3 U. During the last 4 weeks, after the dose had been adjusted, the patients in group D received a total insulin dose of 29 ± 11 U, while the patients in group N received 26 ± 9 U at bedtime (difference NS between groups). The subsequent diurnal blood glucose profiles were lower in both

Table 1—*Effect of combined insulin plus glibenclamide therapy on glycemic control, insulin, C-peptide, serum lipids, and body weight before and after 16 weeks of treatment*

Parameter	Preprandial regular (group D)		Bedtime NPH (group N)		Comparison D vs. N	
	End of study	Change from baseline	End of study	Change from baseline	End of study	Change from baseline
Fasting blood glucose (mmol/l)	10.7 ± 2.6	−2.8 ± 3.5*	7.9 ± 2.3	−6.4 ± 3.0*	$P < 0.0001$	$P < 0.0001$
Mean diurnal blood glucose (mmol/l)	9.6 ± 2.3	−6.6 ± 3.9*	11.1 ± 2.1	−5.1 ± 2.3*	$P < 0.01$	$P < 0.05$
HbA_{1c} (%)	7.1 ± 1.2	−2.1 ± 1.1*	7.5 ± 1.5	−1.7 ± 1.1*	NS	NS
Fasting C-peptide (nmol/l)	0.93 ± 0.31	0.07 ± 0.19†	0.78 ± 0.29	−0.16 ± 0.28‡	$P < 0.05$	$P = 0.0001$
C-peptide at 10 A.M. (nmol/l)	1.18 ± 0.39	−0.03 ± 0.25	1.18 ± 0.38	−0.11 ± 0.36	NS	NS
Fasting plasma insulin (pmol/l)	101 ± 58	18 ± 61	118 ± 43	33 ± 48§	NS	NS
Fasting triglycerides (mmol/l)	1.8 ± 1.3	−0.6 ± 1.1‡	1.9 ± 1.3	−1.0 ± 1.3*	NS	NS
Fasting total cholesterol (mmol/l)	5.7 ± 1.2	−0.3 ± 0.7‡	5.5 ± 0.8	−0.5 ± 0.8§	NS	NS
Fasting HDL cholesterol (mmol/l)	1.3 ± 0.3	0.1 ± 0.3	1.2 ± 0.4	0.1 ± 0.2†	NS	NS
Body weight (kg)	81.2 ± 9.7	3.4 ± 2.1*	80.3 ± 9.5	1.9 ± 1.9*	NS	$P < 0.01$

Data are means ± SD. HDL, high-density lipoprotein. * $P < 0.0001$ vs. baseline. †$P < 0.05$ vs. baseline. ‡ $P < 0.01$ vs. baseline. § $P \leq 0.001$ vs. baseline.

groups (Fig. 1). The profiles differed between the groups in that the patients in group N displayed their lowest blood glucose values in the fasting state, while in group D, the lowest blood glucose values were registered in the afternoon. At the end of the study, FBG was significantly higher and the mean diurnal blood glucose significantly lower in group D compared with group N. HbA_{1c} improved similarly in both groups (Table 1). Of the 76 patients who completed the study, 40 had an HbA_{1c} <7.3% at 16 weeks, i.e., <2% over the reference value or an acceptable HbA_{1c} (8). Twelve patients, two in group D and ten in group N, had FBG <6.7 mmol/l, but no patient exhibited all postprandial values <8.9 mmol/l. The participating patients thus improved their glycemic control, but none of them reached both targets for blood glucose control given in the protocol.

Fasting plasma insulin levels were similar in all three profiles in group D, while a significant increase was seen between baseline and the third profile in group N ($P < 0.001$; Table 1). The insulin levels during the day increased markedly and stepwise for each profile in group D, while the increase in group N was less pronounced (Fig. 1). When calculating the areas under the curves between 0800 and 1900 for plasma insulin, the difference between baseline and the end of study was significant in both groups.

Both groups gained weight significantly during the study, but the weight gain was more pronounced in group D (Table 1). During the first 6 weeks, weight gain did not differ significantly between the groups, but during the last 10 weeks, the patients in group D had a higher rate of weight gain per week, 0.20 ± 0.14 kg/week, as compared with 0.09 ± 0.04 kg/week in group N ($P < 0.01$). There was no correlation between weight gain and the insulin dose or the change in HbA_{1c}. The change in weight was inversely correlated with the body weight before the start of insulin treatment in both groups ($r = 0.46$, $P < 0.0001$ in group D, and $r = 0.60$, $P = 0.0002$ in group N).

CONCLUSIONS — This study demonstrates that the improvement of glycosylated hemoglobin that can be obtained by adding insulin to a maximal dose of glibenclamide in patients with poorly controlled NIDDM is similar whether insulin is given as one dose of bedtime NPH insulin or three preprandial boluses of regular insulin. There is an increase in body weight after initiating insulin therapy in both groups, but this weight gain is more marked in patients treated with preprandial insulin and glibenclamide than in patients receiving a combination of bedtime NPH and glibenclamide. The weight gain is inversely correlated with the patient's body weight before initiation of insulin therapy, but not with the improvement in glycemic control.

Three previous studies have compared the combination of sulfonylurea with one dose of NPH insulin, given either at bedtime or in the morning (2,5,6). These studies have shown that the two regimens are equally effective in lowering glycosylated hemoglobin, but that bedtime NPH is more effective in correcting fasting hyperglycemia. The results of the present study demonstrate that preprandial regular insulin, though giving an unacceptably high FBG, is as effective as bedtime NPH insulin in improving overall glycemic control as determined by HbA_{1c}. Thus, it seems that daytime insulinization has similar effects on overall glycemic control when compared with bedtime NPH, regardless of whether morning NPH or preprandial regular insulin is used.

During the first months of insulin

therapy, NIDDM patients usually gain weight regardless of whether insulin is given alone (2,4,9) or in combination with sulfonylurea (2,5). In this study, both treatment groups showed a significant increase in weight, with a more pronounced weight gain in the preprandial group despite similar insulin doses and effects on glycemic and lipid control. This tendency toward a more marked weight gain when insulin is given during daytime compared with when insulinization is mainly nocturnal has been observed by earlier investigators. In a study by Paterson et al. (10), preprandial doses of regular insulin were compared with one injection of ultralente insulin before dinner without addition of sulfonylurea. Glycemic control improved similarly in the two groups, but the insulin dose was 65% higher in the preprandial group and the patients showed a significant weight gain over the study period. The study by Yki-Järvinen et al. (2) demonstrated that the combination of sulfonylurea with morning NPH insulin caused a more marked weight gain than the combination with bedtime NPH insulin, despite similar doses and similar effects on glycemic control. Our findings suggest that the tendency of a more pronounced weight gain with daytime insulinization than with nocturnal insulinization cannot be circumvented if preprandial regular insulin is used.

We found an inverse correlation between weight gain and pretreatment weight in both groups that has not been described by earlier investigators (4,9). Whether this is due to the fact that nonobese patients in the study might have been more insulin deficient in relative terms may be speculated on. Furthermore, it is not clear to which extent weight gain in our patients reflected an increase of lean body mass. A previous study demonstrated that one-third of the increase in body weight in NIDDM patients during insulin therapy was related to an increase of lean body mass (11).

We conclude that bedtime NPH insulin is, at least initially, a valuable and simple regimen to combine with glibenclamide in NIDDM patients with secondary failure to sulfonylurea. It exerts similar effects on HbA_{1c} and causes less pronounced weight gain than more laborious regimens using preprandial insulin.

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