Repaglinide/Bedtime NPH Insulin Is Comparable to Twice-Daily NPH Insulin

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The combination of oral antidiabetic drugs and bedtime insulin is currently regarded as the first-line therapy in type 2 diabetes. Repaglinide is an insulin secretagogue with a rapid onset and relatively short duration of action (1–3) that was developed for prandial glucose regulation. The prandial glucose regulation strategy attempts to synchronize availability of insulin to the physiological need by stimulating endogenous insulin output in line with glucose intake. In type 2 diabetes, flexible prandial glucose regulation with repaglinide is well tolerated and safe, irrespective of the number of meals consumed per day (4,5). Repaglinide/NPH insulin combination has shown improved glycemic control in type 2 diabetic subjects inadequately controlled by sulfonylureas alone or in combination with metformin (6) or insulin monotherapy (7). However, no direct comparison between repaglinide and NPH insulin combination with NPH twice daily in type 2 diabetic subjects has been reported.

RESEARCH DESIGN AND METHODS — This trial was conducted in 12 sites in Southeast Asia and South Africa. Inclusion criteria included having type 2 diabetes, age ≥18 years, BMI ≤35 kg/m², HbA₁c (A1C) ≥7.5 and ≤13%, previous treatment with sulfonylurea and/or metformin therapy for at least 3 months before study onset (for subjects on sulfonylurea and metformin therapy, metformin dose <1,700 mg/day), and fasting C-peptide >0.33 nmol/l.

During the 3- to 4-week titration period, the initial dose was 1 mg repaglinide at each main meal, which increased to 2 mg (maximum of four meals per day) if fasting plasma glucose (FPG) was ≥7.0 mmol/l. Subjects with FPG ≥8.0 mmol/l were randomized (one to one) to 2 mg repaglinide and bedtime NPH insulin (repaglinide/NPH) or twice-daily NPH insulin (NPH).

RESULTS — Of the 211 subjects enrolled, 54 subjects withdrew during the titration period, mainly (n = 42) due to meeting the exclusion criterion of fasting blood glucose <7 or >15 mmol/l (titration period) or <8 mmol/l (randomization). Sixty-nine percent completed the trial as planned (71 in NPH and 74 in repaglinide/NPH). Twelve subjects withdrew (6 from each group). Two subjects (one from each group) withdrew due to adverse events; both events were judged to be unlikely related to trial products. The remaining 10 subjects withdrew due to noncompliance with protocol/medication, ineffective therapy, and withdrawal of consent.

At screening, the groups were comparable with respect to sex distribution, race, A1C, and FPG but not to age, duration of diabetes, and BMI. At the end of the titration period (baseline), mean A1C was higher in NPH (from 9.1 to 9.4%) but remained unchanged in the repaglinide/NPH group. Sixty-nine percent completed the study period or 8.01 ± 1.0 mmol/l, P = 0.003).

No major hypoglycaemic episodes (blood glucose <2.8 mmol/l) were reported in either group. The incidence of hypoglycaemic episodes was lower in repaglinide/NPH subjects (76 events) than in NPH subjects (206 events), of which >90% were “symptomatic only” in both groups, which translates to a threefold lower risk of hypoglycaemia (reciprocal of relative risk 0.35 [95% CI 0.14–0.78], P = 0.02). The risk of minor hypoglycaemic episodes was not different between treatments (0.45 [0.13–1.31], P = 0.16).
CONCLUSIONS — The efficacy of repaglinide/NPH has been shown to be superior to NPH monotherapy (7,8) and sulfonylurea/NPH (9) but comparable to gliclazide/NPH (10) with similar hypoglycemia profiles. In this study, the efficacy of repaglinide/NPH was comparable to NPH (A1C), whereas the treatment effect on FPG was more pronounced in the NPH group than in the repaglinide/NPH group, which could be due to different injection times in the evening insulin doses between groups. Also, inherent biases in open-label trial design could favor the standard regimen with which doctors are familiar and comfortable. However, a significantly better hypoglycemia profile was achieved with repaglinide/NPH in this study, suggesting that similar glycemic control can be achieved with repaglinide/NPH but at significantly less risk of hypoglycemia. Since repaglinide was developed for use as a prandial glucose regulator, tighter glycemic control through better postprandial glucose control without increased hypoglycemia may be achieved with repaglinide/NPH, but the effects need to be assessed in further studies.

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APPENDIX

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