Safety of Type 2 Diabetes Treatment With Repaglinide Compared With Glibenclamide in Elderly People

A randomized, open-label, two-period, cross-over trial

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The incidence of type 2 diabetes increases with age (1), and elderly people with this disease may be particularly susceptible to hypoglycemia due to long-acting oral antidiabetic drugs (OADs). The American Geriatric Society clinical guidelines on type 2 diabetes treatment in elderly people report that short-acting hypoglycemic agents are preferable to longer-acting agents (chlorpropramide), which are associated with increased risk of hypoglycemia (2). Repaglinide is an insulin secretagogue with a rapid onset and relatively short duration of action (3,4). Several studies have shown repaglinide to be a safe and effective treatment for type 2 diabetes (5–9). However, few data are available on its use in elderly patients and, in particular, on the incidence of hypoglycemic events. The present study assessed the safety of repaglinide versus glibenclamide in this population, in terms of hypoglycemia and adverse events.

RESEARCH DESIGN AND METHODS — This was a 24-week, randomized, open-label, two-period, cross-over comparison between mealtime repaglinide and twice-daily glibenclamide. Patients ($n = 90$) were aged ≥65 years and had been previously treated with diet or OADs (mean age 74.6 years, HbA_{1c} [A1C] 7.9%). A subgroup of 37 patients aged ≥75 years was evaluated separately. After screening, previous OAD treatment was discontinued and patients were randomized to first receive either repaglinide (Novonorm; Novo Nordisk, Bagsværd, Denmark) or glibenclamide (Euglucon; Roche, Basel, Switzerland). Drugs were titrated over a 3-week period to reach optimal dose. Glycemic targets were plasma glucose 6.4–7.2 mmol/l (before meals and at bedtime) and <8.0 mmol/l 2 h after meals (2-h plasma glucose). Repaglinide-treated patients started with 1 mg at each of the three main meals (therapeutic dosage range was between 3 and 6 mg). Patients taking glibenclamide started at 5 mg in two doses, with the second dose before the evening meal (therapeutic dose range was between 5 and 10 mg). Glibenclamide was used at a submaximal dose because of the risk of severe hypoglycemia. The 3-week titration period was followed by a 12-week study period. Patients were then transferred to the alternate drug, with 3 weeks' titration followed by a further 12-week study period.

The primary end point was the number of hypoglycemic episodes during the two-period treatment. Hypoglycemic episodes were defined as any symptomatic episode associated with measured blood glucose <4.0 mmol/l. Hypoglycemia was considered severe when third-party assistance was required. Adverse events (serious or nonserious) were also recorded. Glycemic control was measured by the change in A1C after the two-period treatment from baseline. Changes in fasting plasma glucose (FPG) and 2-h plasma glucose were also assessed. A quality-of-life questionnaire and a MiniMental State Examination were completed at screening and at the end of each arm.

Data are expressed as means ± SD, frequencies, or counts per person-period. Mean changes and count per person-period differences between treatments in the two periods were analyzed using repeated-measures ANOVA via generalized hierarchical linear models (10). Where a carry-over effect was present, the analysis was restricted to the first 12 weeks (11). The whole patient population and patients aged ≥75 years were analyzed. The trial was approved by the local hospitals' ethics committee, and patients gave informed consent.

RESULTS — A total of 88 patients completed the trial. After titration, the mean therapeutic dose was 4.1 mg/day for repaglinide period and 6.1 mg/day for glibenclamide.

The frequency of hypoglycemic episodes (plasma glucose <4.0 mmol/l) was lower with repaglinide than glibenclamide (Table 1). The number of episodes per patient-period was significantly lower with repaglinide (0.38 ± 0.84 vs. 0.81 ± 1.4 per period per patient; $P = 0.002$). This represents a 51% risk reduction (incidence rate ratio [IRR] 0.49 [95% CI 0.33–0.71]) with repaglinide. The proportion of patients having at least one hypoglycemic event was 26.1% with repaglinide and 42.0% with glibenclamide ($P = 0.026$). Also, hypoglycemic episodes, defined as <3.3 mmol/l and <2.7 mmol/l, were lower with repaglinide (Table 1). No carry-over effect for hypoglycemic episodes between treatment arms

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Received for publication 20 December 2005 and accepted in revised form 17 May 2006.

Abbreviations: FPG, fasting plasma glucose; OAD, oral antidiabetic drug.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc05-2495

Table 1

	Repaglinide	Glibenclamide	*P*
Numbers of hypoglycemic symptomatic events associated with glycemia <4.0 mmol/l	33	70	0.0004
Numbers of hypoglycemic symptomatic events associated with glycemia <3.3 mmol/l	24	53	0.0004
Numbers of hypoglycemic symptomatic events associated with glycemia <2.7 mmol/l	10	23	<0.0001
A1C (% at the beginning of each treatment)	7.64 ± 1.4[a]	7.50 ± 1.4[c]	
A1C (% at the end of each treatment)	6.87 ± 1.1[b]	7.14 ± 1.3[d]	
ΔA1C (%)	−0.77 ± 1.0	−0.36 ± 0.9	0.008
FPG at the beginning of each treatment (mmol/l)	7.64 ± 1.3[a]	7.22 ± 1.3[e]	
FPG at the end of each treatment (mmol/l)	6.61 ± 1.1[b]	7.25 ± 1.2[f]	
ΔFPG (mmol/l)	−1.03 ± 1.2	+0.02 ± 1.2	<0.0001
2-h plasma glucose at the beginning of each treatment (mmol/l)	8.93 ± 1.2[a]	8.72 ± 1.2[g]	
2-h plasma glucose at the end of each treatment (mmol/l)	7.98 ± 1.1[b]	8.49 ± 1.1[h]	
Δ2-h plasma glucose (mmol/l)	−0.95 ± 1.3	−0.23 ± 1.4	*

Data are means ± SD unless otherwise indicated. [a] vs. [b], $P < 0.0001$; [c] vs. [d], $P = 0.0005$; [e] vs. [f], $P = 0.77$; [g] vs. [h], $P = 0.11$. *Carry-over and period effect detected; the analysis was thus restricted to the first period only (−0.44 mmol/l in favor of repaglinide [95% CI −1.0 to 0.11]; $P = 0.10$).

was detected. No severe hypoglicemic episodes or adverse events occurred.

In the subgroup of patients aged ≥75 years, 13 and 31 hypoglycemic episodes occurred during repaglinide and glibenclamide treatment, respectively (IRR 0.43 [95% CI 0.23–0.82]). The number of episodes per patient-period for repaglinide and glibenclamide was 0.36 ± 0.7 vs. 0.86 ± 1.5, respectively, $P = 0.04$.

A1C improved significantly after 24 weeks, irrespective of treatment (Table 1). There was a significant difference ($P = 0.008$) in change in A1C between treatments (−0.41% [95% CI −0.71 to −0.11]) in favor of repaglinide (although glibenclamide was submaximally dosed).

FPG and 2-h plasma glucose were also significantly reduced (Table 1). For FPG, a significant difference ($P < 0.0001$) in mean changes between treatments favored repaglinide (−1.05 mmol/l [95% CI −1.38 to −0.33]). For 2-h plasma glucose, since significant carry-over and period effects were detected, analysis was restricted to the first period. The difference between treatments was not significant (−0.44 mmol/l [−1.0 to 0.11]; $P = 0.10$).

In the subgroup aged ≥75 years, similar results were seen. A significant mean change difference in favor of repaglinide versus glibenclamide was shown for A1C (−0.85% [95% CI −1.29 to −0.40]; $P = 0.0006$), FPG (−0.88 mmol/l [−1.61 to −0.22]; $P = 0.01$), and 2-h plasma glucose (−1.0 mmol/l [−1.83 to −0.16]; $P = 0.03$).

There were no significant changes between treatments for other clinical and laboratory parameters. There were also no changes in quality-of-life and MiniMental State Examination evaluations in each treatment arm.

CONCLUSIONS — Fear of hypoglycemia often inhibits the search for good metabolic control in elderly patients with type 2 diabetes. This trial demonstrated that patients aged ≥65 years and ≥75 years treated with repaglinide (up to 6 mg) experienced fewer hypoglycemic events compared with glibenclamide-treated patients, with similar metabolic control. Both the number of hypoglycemic events and the proportion of patients reporting at least one symptomatic event during the treatment period with repaglinide were significantly lower. However, glibenclamide was used at a submaximal dose. Recent clinical practice guidelines suggest individualizing the target A1C in elderly people (2). Our study demonstrates that in patients with borderline poor glycemic control at baseline and in general good health, repaglinide is safe and effective with additional important benefits in terms of lower risk and frequency of hypoglycemia.

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