Clinical Experience with Repaglinide in Patients with Non-Insulin-Dependent Diabetes Mellitus

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Abstract

Background: Repaglinide, a new insulin secretagogue, is purported to be as effective as sulphonylurea but is less hypoglycemic-prone.

Objectives: To assess the efficacy of repaglinide and its proclivity for hypoglycemia in a post-marketing study.

Methods: The study group comprised 688 patients, aged 26–95 years, clinically diagnosed with non-insulin-dependent type 2 diabetes. The patients were divided into three groups based on previous therapy: a) sulphonylurea-treated (group 1, n = 132); b) metformin with or without sulphonylurea where sulphonylurea was replaced with repaglinide (group 2, n = 302); and c) lifestyle modification alone (drug-naïve) (group 3, n = 254). At initiation of the study, all patients were transferred from their current treatment to repaglinide. Only patients in group 2, with combined sulphonylurea plus metformin, continued with metformin plus repaglinide. Fasting blood sugar, hemoglobin A1c and weight were measured at study entry and 4–8 weeks following repaglinide therapy. A questionnaire documented the number of meals daily and the presence of eating from fear of hypoglycemia.

Results: The fasting blood sugar level of the entire cohort dropped from 191 ± 2.4 to 155 ± 2.0 mg/dl ($P < 0.0001$); HbA1c from 8.8 ± 0.1 to 7.7 ± 0.1% ($P < 0.0001$). The drop of HbA1c in groups 1, 2 and 3 respectively were: 1.04 ± 0.22% ($P < 0.0001$), 1.14 ± 0.24% ($P < 0.0001$), and 1.51 ± 0.31% ($P = 0.0137$). Weight dropped from 81 ± 0.7 to 80.2 ± 0.7 kg ($P < 0.0001$), and eating from fear of hypoglycemia from 157 to 97 ($P < 0.001$). The daily number of meals decreased from 2.9 ± 0.4 to 2.4 ± 0.4 ($P < 0.001$). No serious adverse reactions occurred during the study.

Conclusions: Repaglinide is an effective oral hypoglycemic agent taken either as monotherapy or combination therapy. There is less eating to avoid hypoglycemia, fewer meals consumed, and weight loss.

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Repaglinide, a phenylalanine derivative, is the first secretagogue of the metaglinide group. Its mode of action involves interaction with voltage-dependent K-ATP channels on beta cells with subsequent release of insulin. Compared to the sulphonylureas, repaglinide-induced release of insulin is faster and of shorter duration. These qualities afford greater control of postprandial glucose elevations and diminish the frequency of hypoglycemic reactions [1–3]. Several studies have also shown that in terms of efficacy this agent is equivalent to the sulphonylureas and has fewer hypoglycemic events [4,5]. Moreover, repaglinide exhibits a highly selective affinity profile to the beta cells [6].

We present the results of a post-marketing study in 688 patients receiving repaglinide as monotherapy or in combination with metformin.

Patients and Methods

Patients

We enlisted 688 patients with clinically diagnosed NIDDM, not treated with insulin, from the practices of 97 family physicians and 12 diabetologists. Patients treated with insulin and patients with satisfactory diabetic control (HbA1c <7%) were excluded. Since this was a post-marketing study no parallel control group was included and the patients served as their own control. Baseline parameters were collected retrospectively at visit 1 and served as the basis for the effectiveness of evaluation of repaglinide treatment. Of the 688 who were recruited, 621 (322 males and 299 females) completed the survey. Patient drop-out was not associated with adverse reactions to repaglinide. The total patient population was divided into 10 year age groups ranging from 26–35 to 86–95 years [Table 1]. The majority of patients were in the 56–65 year old age group (35%).

Patients were also divided into three groups according to other oral hypoglycemic agents administered before the study:

- Patients originally receiving sulphonylureas who were switched to repaglinide (n=132)
- Patients receiving metformin or a combination of metformin plus sulphonylureas (n=302). Patients who received metformin as a monotherapy started with repaglinide, while repaglinide replaced sulphonylureas in the other patients on combination therapy.
- Patients who were treated previously only with diet and exercise at all times (drug-naive). These patients were assigned to repaglinide as a monotherapy (n=254).

Protocol

Patients were clinically evaluated for type of diabetes, level of control, and modalities of treatment. Fasting blood sugar, HBA1c and weight were measured at baseline (visit 1) and 4–8 weeks following initiation of therapy with repaglinide (visit 2). Initially, patients were scheduled for 4 weeks after the initial treatment visit

Table 1. Patients' age groups

Age group	Total no. of patients	%
No age given	7	1%
26–35	13	2%
36–45	85	12%
46–55	182	26%
56–65	235	35%
66–75	134	19%
76–85	27	4%
86–95	5	1%
Total	688	100%

However, due to failure of many patients to show up at scheduled appointments, evaluation was deferred for an additional 4 weeks. Data of all treated patients were included in the analysis. Doses of repaglinide were started at 0.5 mg before each meal and titrated according to blood glucose level. All patients were given a questionnaire and asked to document their eating habits and specifically the need to eat from fear of impending hypoglycemia, prior to and following repaglinide administration

Laboratory techniques

Plasma glucose was measured with a glucose oxidase technique. HbA1c was measured with a standard kit using immunoassay and spectrophotometric techniques.

Statistics

All laboratory values are expressed as mean ± SEM. The mean ± SEM values were compared using the *t*-test. *P* value of <0.05 was considered statistically significant. All statistical data were calculated with SAS software.

Results

Mean fasting blood sugar at the first visit was 191.0 ± 2.4 mg/dl and on the second visit 154.9 ± 2.0 mg/dl, with a total reduction of 36.1 ± 0.7 mg/dl ($P < 0.0001$). The average decreases in blood sugar were seen in every age group and ranged from 18.4 to 43.7 mg [Table 2].

The mean drop of HbA1c at visit 2 (end of repaglinide treatment) as compared to visit 1 (different drug regimens prior to initiation of repaglinide) was 1.04 ± 0.22% ($P < 0.0001$) in group 1 (sulphonylurea group), 1.14 ± 0.24% ($P < 0.0001$) in group 2 (metformin group), and 1.51 ± 0.31% ($P = 0.0137$) in group 3 (naive group). The mean weight for all patients was 81.3 ± 0.7 kg at the initial visit and 80.2 ± 0.7 kg at the second visit. The mean weight reduction was 1.1 ± 0.3 kg ($P < 0.0001$).

With regard to the presence of eating from fear of hypoglycemia, 157 patients from groups 1 and 2 receiving sulphonylureas at baseline answered "present" at the first visit. This number dropped to 97 at the second visit (38.2% reduction, $P < 0.001$). Furthermore, when given the opportunity to skip a meal or to avoid snacking between meals, patients on repaglinide treatment reduced the average daily number of meals to 2.4 ± 0.4 as compared to 2.9 ± 0.4 at visit 1 ($P < 0.001$)

Table 2. FBG on visit 1, visit 2 and the differences

Age	Visit 1 FBG (mg/dl)		Visite 2 FBG (mg/dl)			
group	Mean	SEM	Mean	SEM	Difference	*P*
26–35	193.9	13.4	152.8	9.9	-41.1	0.009
36–45	199.5	8.4	155.8	6.3	-43.7	0.000
46–55	202.5	4.8	162.6	4.4	-39.9	0.000
56–65	188.7	4.0	153.1	3.1	-35.6	0.000
66–75	174.7	4.4	146.9	3.5	-27.8	0.000
76–85	181.2	13.9	162.7	16.7	-18.4	0.110
86–95	166.3	7.3	125.3	16.7	-41.0	0.163
Total	191.0	2.4	154.9	2.0	-36.1	0.000

The range of the mean HBA1c in the various age groups varied from 7.4 ± 0.4 to 9.5 ± 0.3% on the first visit and dropped to 6.4 ± 0.06 to 8.2 ± 0.2% on the second visit [Table 3]. The mean HbA1c at the initial visit was 8.8 ± 0.1 and 7.7 ± 0.1% at the second visit with a difference of 1.1 ± 0.1% ($P < 0.0001$).
FBG = fasting blood glucose

Table 3. HbA1c on first visit (V1), second visit (V2) and the differences

Age	Visit 1 FBG HbA1c (%)		Visite 2 FBG HbA1c (%)			
group	Mean	SEM	Mean	SEM	Difference	*P*
26–35	9.1	0.7	7.8	0.5	-1.3	0.026
36–45	9.5	0.3	8.2	0.2	-1.2	0.000
46–55	9.0	0.1	7.8	0.1	-1.2	0.000
56–65	8.7	0.1	7.6	0.1	-1.1	0.000
66–75	8.4	0.1	7.4	0.1	-1.0	0.000
76–85	8.2	0.3	7.1	0.2	-1.1	0.011
86–95	7.4	0.4	6.4	0.06	-1.0	0.141
Total	8.8	0.1	7.7	0.1	-1.1	0.000

There were no reports of serious adverse reactions, including major hypoglycemic events, occurring during the period of the study.

Discussion

This study reflects the clinical experience with repaglinide as reported by physicians in real-life practice. The average drop in fasting blood glucose and HbA1c noted in this study is comparable to that in other studies carried out under more rigorous conditions [7,8]. The present study confirms that when used in a real-life setting, repaglinide is an effective agent for controlling glucose levels in a heterogeneous population as mono- or combined therapy.

The response of repaglinide in naive patients appears to be greater than in those receiving a sulphonylurea. A potential explanation for this phenomenon is that chronic sulphonylurea stimulation of the beta cells may lead to desensitization [9].

Another positive finding of this survey was the drop in frequency of perceived appearances of hypoglycemia and the need for food intake to avert this event in patients previously taking sulphonylureas. This is reflected in the reduced average number of daily meals and the average weight reduction while taking repaglinide, without compromising the improvement in metabolic control [10]. Other studies have also shown that hypoglycemia and weight gain occurred in repaglinide-treated patients but the magnitude was

significantly less than in sulphonylurea-treated patients [11]. More than 58% of the patients in this study were over 55 years old; these are the patients in whom hypoglycemic reactions are most deleterious and may lead to injurious cardiovascular events [12]. Since repaglinide is taken with the meal it allows the freedom to eat when desired and not from fear of hypoglycemia. Under such a regimen patients can manage a flexible lifestyle, eat whenever they want, avoid the need for snacking, and have the choice to skip a meal without the risk of suffering a hypoglycemia event as a result.

Conclusion

Repaglinide is an oral hypoglycemic agent that offers improved glycemic control; it has a safe profile and the advantages of flexibility and convenience in terms of meals and snacks for the heterogenic population of type 2 diabetics, and no undesirable body weight gain.

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The rule about rules is there are no rules

Aristotle Onassis (1906-73), Greek shipping tycoon, who owned the largest independent line in the world and was the first to construct supertankers. A determined and tireless entrepreneur, his huge success was partly due to his disregard for rules and his ability to circumvent the law, including whaling in restricted waters. In 1968 he married Jacqueline Kennedy after a long relationship with the diva Maria Callas.

Capsule

Treating Crohn's disease with worms

Crohn's disease is a debilitating inflammatory condition of the intestine. Although the etiology is unclear, the disease is thought to result from inappropriate activation of the immune system against the bacterial flora of the gut. In developing countries, where infection with parasitic intestinal helminths is widespread, Crohn's disease is rare, leading to the notion that the allergic-like state generated by parasitic worms counteracts pro-inflammatory influences. To test this, Summers et al. (*Gut* 2005;54:87) fed Crohn's patients eggs of the common pig helminth *Trichuris suis*, which can colonize the human intestine for short periods without pathology. A marked improvement was seen in most of the patients, and these clinical results are paralleled by the observations of Elliott et al. (*Eur J Immunol* 2004;34:2690) who found that giving the helminth *Heligmosomoides polygyrus* to mice that were afflicted with a Crohn's-like condition reversed inflammation. In protected animals, there was a redress of the imbalance toward pro-inflammatory cytokines, and these early results suggest that unconventional therapy of this type might be effective in treating a range of chronic inflammatory diseases that extend beyond the gut.

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