The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus

Rodolfo Guardado-Mendoza¹, Annamaria Prioletta¹(†), Lilia M. Jiménez-Ceja¹, Aravind Sosale³, Franco Folli皮肤

Abstract

Type 2 diabetes mellitus (T2DM) is one of the most common chronic diseases worldwide, presenting a great challenge to the public health systems due to high morbidity and mortality, because of frequent micro-/macro-vascular complications. Many treatment options are now available, with different efficacy as well as mechanisms of action to improve deranged glucose metabolism. We review some of the available data on derivatives of meglitinide, namely nateglinide and repaglinide. These two compounds increase insulin secretion by a mechanism similar to the one of sulfonylureas, but with a shorter half-life. Nateglinide and repaglinide, derivatives of meglitinides, have characteristic pharmacodynamic and pharmacokinetic properties that, together with their proposed mechanism of action, make them useful for type 2 diabetes mellitus, especially when used in combination therapy.

Key words: meglitinide, repaglinide, nateglinide, glycemic control, post-prandial glucose excursion, hypoglycemia.

Data sources

We performed a systematic Medline search (from September 2012 to December 1994), using the following search terms:

- “meglitinide analogues” and/or “nateglinide” or “repaglinide”,
- “repaglinide and sulfonylureas”,
- “nateglinide and sulfonylureas”.

Eighty-two papers considered relevant for the aim of this review were selected by the authors. When previous systematic reviews were incorporated, we independently examined the individual studies to confirm or extend previous reviews’ findings.

Chemical and pharmacodynamic properties

The meglitinide analogues are insulinotropic agents, introduced in 1995 and approved for clinical use in adults with type 2 diabetes mellitus (T2DM) in 2000. They are secretagogue molecules with a more rapid anti-hyperglycemic action and a shorter duration than sulfonylureas, thus providing...
better control of post-prandial hyperglycemia and reducing the risk of late hypoglycemia [1, 2].

**Repaglinide**

Repaglinide was the first meglitinide analogue approved for clinical use in adults with T2DM. Repaglinide is the S(+) enantiomer of 2-ethoxy-4-((3-methyl-1-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid with a molecular weight of 452.6 Da.

The mechanism of action is similar to sulfonylureas, but repaglinide exhibits distinct pharmacological properties in structure, binding profile, duration of action and mechanisms of excretion [3].

Like the sulfonylureas, the insulinotropic action of repaglinide is mediated via adenosine triphosphate (ATP)-dependent potassium channels. Repaglinide stimulates insulin secretion by blocking ATP-dependent potassium channels (KATP) of the pancreatic β-cell, where inhibition of KATP channels results in membrane depolarization and calcium influx through voltage-gated calcium channels. These events lead to an increase in intracellular calcium and subsequent exocytosis of insulin-containing granules.

The KATP channel is a hetero-octameric complex of two different types of protein subunits: an inwardly rectifying K+ channel (Kir) subunit 6.x and a sulfonylurea receptor (SUR). More than one isoform exists for both Kir6.x (Kir6.1, Kir6.2) and SUR (SUR1, SUR2A, SUR2B). Distinct isoforms and splice variants of the SUR subunit are expressed in different tissues and confer many of the pharmacological properties to the KATP channel hetero-octamer. The subunits that are predominantly expressed in pancreatic β-cells are Kir6.2 and SUR1 [4].

Repaglinide binds to the sulfonylurea receptor SUR1 and it seems to have also a separate distinct binding site on β cells, as demonstrated in mouse β cells co-incubated with PPP (3-(3-hydroxyphenyl)-N-(1-propyl) piperidine), a pharmacological tool to differentiate between the two different binding sites [5]. Moreover, molecular studies have shown that the binding site of repaglinide is different from that of glibenclamide and nateglinide [6].

**Nateglinide**

Nateglinide is a (N-[(trans-4-isopropylcyclohexyl)-carbonyl]-D-phenylalanine A-4166) phenylalanine derivative. Like repaglinide, also nateglinide binds competitively to SURs, inhibiting KATP channels and stimulating insulin secretion, but the pharmacodynamic properties of this molecule are unique in several aspects [7].

Comparative preclinical studies in vivo indicate that nateglinide inhibits KATP channels more rapidly, and with a shorter duration of action, than glibenclamide, glimepiride and repaglinide, and shows a greater degree of specificity for SUR1 over SUR2, as compared with glibenclamide and repaglinide. Also, the half-life of nateglinide on the receptor is approximately 2 s, much shorter when compared to that of repaglinide, which is ~3 min. In addition, the dissociation from the receptor is estimated to be 90 times faster than that of repaglinide, indicating a very short on-off effect of nateglinide on insulin release [8].

Foley et al. have demonstrated a sort of “glucose-sensitizing property” of nateglinide in in vitro experiments on rat β cells. In fact, unlike glibenclamide and repaglinide, the potency of nateglinide increases in the presence of glucose. The inhibition of KATP current is enhanced 16-fold when the glucose concentration is raised from 3 mmol/l to 16 mmol/l. Interestingly, the glibenclamide potency is much reduced under these conditions, whereas the potency of repaglinide is enhanced 4-fold only, which could explain the low incidence of hypoglycemia [8].

Moreover, pharmacodynamic studies in patients with T2DM have demonstrated that the administration of nateglinide (prior to meals) induces early phase insulin secretion and significantly reduces post-prandial hyperglycemia in a dose-dependent manner. Interestingly, insulin secretion was significantly greater when nateglinide was taken before a meal compared to nateglinide given in the fasted state or in response to just the meal [9].

**Pharmacokinetic properties**

**Repaglinide**

Repaglinide is rapidly absorbed after oral administration. The peak plasma concentration is reached 30-60 min after administration, plasma levels decrease rapidly and the drug is eliminated within 4-6 h. Its absorption is not affected by food, the bioavailability is 63% and the half-life is ~1 h [10].

Repaglinide has a small volume of distribution and is highly bound (more than 98%) to plasma albumin. Repaglinide is metabolized by the liver cytochrome P450 (CYP3A4) and eliminated rapidly throughout the biliary tract, without apparent accumulation in the plasma after a multiple dose [11].

Around 90% of the metabolites are excreted throughout the bile and only 8% can be traced in the urine. Only 2% of repaglinide is eliminated as unchanged and its metabolites are not biologically active and they do not have a blood glucose lowering effect.

In vitro studies have shown that substances which inhibit the enzyme CYP3A4, such as ketoconazole, anti-bacterial agents, steroids and cyclosporine, may reduce metabolism and increase repaglinide concentration, while drugs which induce CYP3A4, such as rifampicin, carbamazepine, and barbiturates, may accelerate repaglinide metabolism [11].
Nateglinide

Nateglinide is rapidly absorbed after oral administration from the gastrointestinal tract in a dose-dependent manner and the bioavailability of the drug is approximately 72% [12]. The optimal time of oral administration of nateglinide is before the meal; in fact absorption is more rapid when the drug is administered 0-30 min before meals [13]. Peak plasma concentrations are achieved within 1 h and the half-life is 1.8 h because it is rapidly eliminated from plasma. This short elimination half-life ensures no drug accumulation at any dose level. Nateglinide is metabolized mainly via the hepatic CYP2C9 and CYP3A4 isoenzymes of cytochrome P450 and eliminated primarily by the kidney. Twenty percent of a nateglinide dose is eliminated unmodified in the bile and 10% in the urine [12]. Nateglinide is also extensively bound to plasma proteins (98%) and has a relatively small volume of distribution [12].

Indications and dosage

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated the clinical importance of good glycemic control in the prevention of chronic vascular complications of T2DM, but also the limited long-term efficacy of drugs such as sulfonylureas, metformin, and acarbose, none of which proved capable of preventing a progressive increase in HbA1c levels after an initial response [14]. The progressive nature of T2DM usually requires a combination of two or more oral agents, eventually followed and combined GLP-1 analogues, and finally insulin in the longer term.

The European Association for the Study of Diabetes-American Diabetes Association (EASD-ADA) Consensus Algorithm recommends the use of metformin as first line treatment in most patients, with the addition of other drugs to achieve adequate glycemic control, i.e. HbA1c < 7%. Treatment choice should rely on the mechanism of drug action, efficacy and safety [15-17].

Post-prandial glycemia contributes to mean glucose and to HbA1c levels, and therefore good control of post-prandial glycaemia is a key element in the maintenance of HbA1c levels < 7%. There is also evidence suggesting that post-prandial hyperglycemia could represent a significant independent risk factor for diabetic macrovascular and microvascular complications in both T1DM and T2DM, also possibly because of increased oxidative stress [18-25].

Currently available hypoglycemic medications are all able to reduce HbA1c level although to a different extent, but only a few of them can specifically reduce post-prandial glycemia [26-29].

Meglitinide analogues, acting on the pancreatic β cells, mimic somehow the early rise of insulin secretion after meal ingestion and reduce post-prandial hyperglycemia [2]. Clinical trials of nateglinide and repaglinide have shown efficacy and safety as monotherapy and in combination therapy in patients with T2DM.

The short-acting insulin secretagogues are well suited for patients with T2DM who would like to have a more flexible lifestyle and who have problems adhering to more rigid therapeutic regimes. In fact, administering short-acting insulin secretagogues immediately prior to meals increases patient compliance and flexibility in calorie intake and dietary adherence [26].

Both nateglinide and repaglinide have a good safety profile. Moreover, repaglinide is eliminated mainly via non-renal routes and can therefore be administered to patients with mild to moderate renal insufficiency and/or in whom one of the other second-line anti-hyperglycemic drugs is contraindicated [30].

In clinical trials in T2DM, repaglinide was usually administered at a dosage of 0.5-4 mg three times daily before meals as monotherapy or in combination with other agents and no dosage adjustment was necessary in mild and moderate renal impairment [31, 32].

During clinical development, and in clinical trials, nateglinide has been well tolerated. The insulin secretory response progressively increased after single doses of nateglinide up to 180 mg, and in another study, 120 mg was the maximally effective nateglinide dose for lowering glucose without the occurrence of hypoglycemia [9].

Clinical efficacy

Randomized, double-blind controlled trials have shown that nateglinide 360 mg/day significantly improves long-term glycemic control in patients with T2DM by reducing HbA1c levels by 0.4-0.8% [33-35]. Compared with placebo, HbA1c values are approximately 1% lower after nateglinide therapy [1, 34, 36]. When comparing repaglinide 1.5 mg/day and nateglinide 180 mg/day as monotherapy, in a 16-week study, the reduction in HbA1c values from baseline was significantly greater for repaglinide than nateglinide (1.57% vs. 1.04%), and repaglinide had more pronounced effects on reducing fasting plasma glucose and glucagon secretion, with no differences in post-prandial glucose and insulin secretion [37].

Different studies have compared the efficacy of glinides and sulfonylureas. A study comparing the effects of 270 mg of nateglinide (n = 16) with 20 mg of gliclazide (n = 8) in a 12-week open label prospective study found that gliclazide was slightly more effective than nateglinide (HbA1c 0.2% less in the gliclazide group) [38]. A small and short duration study (n = 47, 4 weeks duration) also showed sim-
ilar results comparing repaglinide 3.6 mg/day vs. glipizide 54 mg/day on glycemic control and insulin secretion [39]. A double-blind, placebo-controlled trial compared the effects of repaglinide vs glimepiride therapy, with the dose of drugs optimized, showing the same reduction of HbA1c and control of fasting glucose and post-prandial hyperglycemia after a 12-month treatment period [40].

A dose of 6 mg/daily of repaglinide showed an efficacy comparable to 2 g of metformin on fasting and integrated 6-h post-prandial measures of plasma glucose, triglycerides and serum free fatty acids in 96 non-obese T2DM patients during a 4-month crossover study [41]; in a 24-week multicenter study 360 mg of nateglinide was similarly effective to metformin 500 mg three times a day in terms of HbA1c reduction (–0.8% in both groups) [34, 36].

When added to metformin, nateglinide at a dosage of 360 mg/day caused an HbA1c reduction of approximately 0.4-0.8% [34, 36, 42], with a few studies reporting no differences between groups [43]. Metformin + nateglinide 540 mg/day was similarly effective to metformin + glipizide 240 mg/day during a 24-week period (HbA1c reductions of 0.41% and 0.57%, respectively). Notably, the metformin + nateglinide combination produced a more pronounced effect on post-prandial glucose than the metformin + glipizide combination, and the latter had a better efficacy on fasting plasma glucose, with no differences in the rate of hypoglycemic events; however, when the study was extended to 1 year duration, the glipizide group showed a slightly larger reduction of HbA1c (–0.27 vs. –0.14) [44, 45]. When nateglinide + metformin was compared to glibenclamide + metformin, most of the studies have reported similar reduction of HbA1c (1.0-1.5%), but some of them have reported a greater effect of the nateglinide + metformin combination (HbA1c reduction 0.8% greater than the glibenclamide + metformin combination), confirming also that the nateglinide + metformin combination was more effective in reducing post-prandial plasma glucose, and the glibenclamide + metformin combination in improving fasting plasma glucose [46-49].

In a 24-week randomized clinical trial, the addition of 360 mg of nateglinide to 8 mg of rosiglitazone treated patients provided an additional reduction of HbA1c of 0.8% [50].

Other studies have also demonstrated that glinides can be employed in combination with insulin. Repaglinide + bedtime NPH (n = 74) was compared to twice-daily NPH insulin (n = 71), revealing no differences in terms of HbA1c, but at the same time they found a greater decrease in fasting plasma glucose in the NPH group (122 mg/dl vs. 144 mg/dl) [51]. In a 24-week randomized study, the combination of repaglinide + metformin + NPH (n = 12) had a higher decrease in HbA1c when compared with groups of metformin + NPH (n = 12) and NPH + NPH (n = 13) (7.2% vs. 8.8% and 8.4%, respectively) [52]. In a 1-year randomized double-blind parallel study, repaglinide + biphasic insulin aspart (70/30) was similarly effective to metformin + biphasic insulin aspart to achieve a 1% HbA1c reduction in non-obese diabetic patients [53]. Adding nateglinide before meals to once-daily insulin glargine in people with long-standing diabetes provides only a slight improvement in glucose control during the first part of the day, without any improvement on the overall glucose control [54].

Recently, the effect of glinides on the gastrointestinal incretin system has been investigated. It has been hypothesized that some of the beneficial actions of glinides may be indirectly mediated through dipeptidyl peptidase-IV (DPP-IV) inhibition. Dipeptidyl peptidase-IV is a ubiquitous enzyme that rapidly degrades the incretin hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Studies in humans have shown that nateglinide can inhibit DPP-IV, thereby increasing GIP levels [55], while other have reported no effect on the incretin levels [56]. The combination of nateglinide and GLP-1 improved glycemic control, increasing insulin and GLP-1 levels, as compared with nateglinide or GLP-1 alone, suggesting also that nateglinide had an inhibitory effect on the activity of DPP-IV or a stimulatory effect on GLP-1 secretion [57]. A study in rodents showed that promotion of GLP-1 release from intestinal L cells may be an additional mechanism by which nateglinide restores early-phase insulin secretion [58].

**Role of glinides on the physiopathological abnormalities in type 2 diabetes mellitus**

Multiple physiopathological abnormalities have been described in T2DM, including liver and muscle insulin resistance, beta and alpha cell dysfunction and incretin defect [59, 60]. The long-term efficacy of the available drugs is dependent on the impact of each one of them on the known physiopathological abnormalities of the disease. From this point of view, glinides mainly impact on the insulin secretion defect and possibly may have some effect on the increased glucagon secretion [37], and a few studies have suggested that glinides may also have some positive effect on the incretin system, by increasing the levels of GLP-1, especially when combined with GLP-1 [55, 57, 58].

**Tolerability profile**

**Hypoglycemia**

In most clinical trials, repaglinide and nateglinide treatment caused a low incidence of subjective symptoms of hypoglycemia [61-64].
Marbury et al. in a 1-year comparative trial demonstrated a similar rate of hypoglycemic events during repaglinide versus glibenclamide therapy and Madsbad et al. in a comparative study of repaglinide vs glipizide treatment did not demonstrate in either group any major hypoglycemic event and the number of patients experiencing minor hypoglycemia was similar in the repaglinide and glipizide groups [61, 62].

No severe hypoglycemic episodes occurred in patients treated with repaglinide plus metformin in a randomized study in naïve T2DM patients, and combination therapy with repaglinide plus metformin resulted in fewer hypoglycemias than combination therapy with sulfonylureas [63, 64]. Repaglinide caused fewer hypoglycemias than glibenclamide also in elderly patients, as demonstrated by a small randomized crossover study in elderly patients [65].

Finally, repaglinide is safe and well tolerated in subjects with varying degrees of renal impairment. The incidence of hypoglycemic events did not differ between patients with renal dysfunction and healthy subjects who received repaglinide 2 mg three times daily [30].

Nateglinide is associated with a low risk of hypoglycemic events in placebo-controlled or active-controlled studies [49, 66].

Bellomo Damato et al., in a recent double-blind randomized study comparing nateglinide 120 mg three times daily with glyburide 5 mg once daily, demonstrated that nateglinide is associated with a lower risk of hypoglycemia than glyburide [66]. A double blind, multicenter, randomized study that aimed to assess the efficacy and tolerability of nateglinide alone or in combination with metformin in elderly patients with T2DM demonstrated that nateglinide monotherapy (120 mg) did not cause any serious hypoglycemic episodes. In the nateglinide/metformin arm there was one mild hypoglycemic episode compared with eight episodes in the glyburide/metformin arm [49].

Studies directly comparing repaglinide and nateglinide have been lacking and it is therefore not possible to assess their differences in term of clinical efficacy and safety [37, 67]. No major hypoglycemic episodes and no reported minor hypoglycemic events were found in the nateglinide group in a randomized, multicenter study, where patients were randomized to receive monotherapy with repaglinide (0.5 mg/meal, maximum dose 4 mg/meal) or nateglinide (60 mg/meal, maximum dose 120 mg/meal) for 16 weeks [37]. An open-label, parallel-group, randomized trial conducted to compare efficacy and safety of repaglinide vs. nateglinide in a combination regimen with metformin did not show any significant differences between the two treatment groups in terms of hypoglycemic event frequency [67].

**Body weight**

Body weight change was a secondary endpoint in several clinical trials with repaglinide and nateglinide [31, 68, 69]. In a multicenter, double-blind, placebo-controlled study, aimed to assess the efficacy and safety of repaglinide compared with placebo in type 2 diabetes patients, Goldberg et al. demonstrated only a small non-significant increase in body weight [31]. A multicenter, double-blind trial to compare the effect of repaglinide in combination with metformin in patients not controlled by metformin alone demonstrated an increase in body weight in the repaglinide group [68].

In another randomized, parallel-group study, comparing repaglinide and glibenclamide, the repaglinide group showed less weight gain than those treated with glibenclamide, over 1 year of treatment [62]. In a study aimed to compare the metabolic effects of add-on therapy with acarbose and repaglinide in patients treated with a sulfonylurea-metformin combination therapy, at the same glycemic control, the repaglinide group presented a significant increase in body weight [70].

Also nateglinide treatment was associated with a small body weight increase in most clinical trials. In the NAVIGATOR trial, conducted on subjects with impaired glucose tolerance, subjects treated with nateglinide did not show a significant increase in body weight as compared to the control group [71]. Only a modest increase in body weight was observed in diabetic patients receiving three fixed doses of nateglinide compared with placebo-treated patients [69].

Direct comparison trials of repaglinide and nateglinide to assess change in body weight have been few. In a multicenter study comparing monotherapy with repaglinide or nateglinide for 16 weeks, mean weight gain at the end of the study was 1.8 kg in the repaglinide group as compared with 0.7 kg for the nateglinide group [37].

**Cardiovascular safety**

Meglitinide stimulates insulin secretion by closing of KATP channels in β cells. KATP channels are ubiquitously present in extrapancreatic tissues including heart, central nervous system, skeletal muscle and smooth muscle. KATP channels are also abundant in both cardiomyocytes, where they are involved in the mechanisms of adaptation of the heart to ischemic stress, and arterial smooth muscle cells, regulating coronary blood flow [72].

Sulfonylureas and meglitinide analogues, binding to pancreatic β-cell KATP channels, may also bind to KATP channels of cardiomyocytes and vascular smooth muscle cells, possibly leading to impairment of ischemic preconditioning. Suggestions
about the possibility of worse clinical outcomes because of sulfonylureas treatment emerged from a post-hoc analysis of the DIGAMI study, but the UKPDS data did not support the suggestion of adverse cardiovascular effects of sulfonylureas [14, 73]. As reported above [5, 6], the meglitinide analogs bind to KATP channels at a different site and they have much shorter half-lives than do sulfonylureas, and this minimizes their potential negative effects on the heart. Repaglinide and nateglinide show different selectivity for KATP subtype. Nateglinide has a greater degree of specificity for SUR1 over SUR2, as compared with glibenclamide and repaglinide, and is up to 1000-fold more selective for the pancreatic KATP subtype than the cardiovascular subtype, while repaglinide is non-selective for the pancreatic KATP subtype [7, 8].

However, repaglinide treatment has not been shown to be associated with increased mortality and cardiovascular risk compared with metformin in a large cohort of diabetic patients with or without previous myocardial infarction [74]. In an open uncontrolled randomized study involving 112 patients with inadequately controlled type 2 diabetes not previously treated with oral hypoglycemic agents, the use of repaglinide was associated with improvements in cardiovascular risk profile [74, 75]. The NAVIGATOR study, conducted to evaluate the ability of nateglinide to reduce the risk of diabetes and cardiovascular events in people with impaired glucose tolerance, failed to demonstrate a reduction in diabetes incidence and cardiovascular events [71, 76].

Pancreatic β cell failure and meglitinide

Studies in β-cell line and rodent islets demonstrated that glibenclamide and tolbutamide may induce, Ca2+ dependently, β-cell apoptosis, and this finding was confirmed in a recent study conducted also in human islets [77, 78].

Although meglitinide analogues have similar effects to glibenclamide in terms of insulin secretion stimulation, it appears that nateglinide and repaglinide are less toxic for β cells, as widely reported in the recent review of Blickle et al. [79].

Animal studies also suggest that nateglinide reduces the risk of insulin depletion compared with glibenclamide [80]. Moreover, in vitro exposure of human islets to nateglinide did not increase the β-cell apoptosis rate and, consistent with this observation, repaglinide had no deleterious effects on β-cell survival [81, 82].

Conclusions

Nateglinide and repaglinide are effective in reducing post-prandial glucose excursion and HbA1c levels by 0.8% to 1% in T2DM. We believe that the main role of glinides as a therapeutic option in T2DM is in combination with other drugs, since the treatment must be focused on the different mechanism of action of each drug. Glinides share some of the pharmacological properties with sulfonylureas, but show interesting differences with regards to their particular mechanism of action. Glinides stimulate insulin secretion with a very short half-life, which confines them the advantages of not causing excessive hypoglycemia, weight gain and chronic hyperinsulinemia, which are more common with sulfonylureas.

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