

Recent Developments in the Pharmacological Reduction of Blood Glucose in Patients With Type 2 Diabetes

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The options available to practitioners managing hyperglycemia in patients with type 2 diabetes remained relatively static for 45 years. Until 5 years ago, the only options available were sulfonylureas, insulin, or sulfonylurea/insulin combinations. Before that, the biguanide phenformin was introduced briefly to the market, but its use in this country was ephemeral because of its association with lactic acidosis.¹

In the past 5 years, diabetology has witnessed the introduction of a multitude of new medications, including α -glucosidase inhibitors, a biguanide, the thiazolidinediones, insulin analogs, meglitinides, and d-phenylalanine derivatives. These new agents have dramatically increased the number of options available to providers and patients. Combination therapy has become commonplace for the management of hyperglycemia in patients with type 2 diabetes. This article briefly reviews some of the more recent pharmacological advances.

Insulin-Sensitizing Agents

Two categories of compounds that reduce insulin resistance are available in the United States: the biguanides and the thiazolidinediones. The only formulation containing a biguanide was metformin (Glucophage) until recently, when the Food and Drug Administration (FDA) approved a new combination glyburide/metformin hydrochloride tablet (Glucovance) and an extended-release form of metformin (Glucophage XR). Additionally, two thiazolidinedione compounds are available: pioglitazone

(Actos) and rosiglitazone (Avandia). While several other thiazolidinedione compounds are under investigation, no new compounds have been released during the past 2 years.

Glyburide/metformin combination tablet

The FDA recently announced its approval of this new formulation containing metformin and glyburide in a single tablet. It is well documented that type 2 diabetes is a disease resulting from two impairments: a relative insulin deficiency accompanied by insulin resistance.² Simultaneous initiation of complementary compounds that address the two known impairments of type 2 diabetes is logical. By treating both impairments early, better glycemic con-

trol may be achieved, ultimately resulting in a reduction in chronic complications.

The initial phase III trials with metformin demonstrated that when patients were no longer responding to glyburide therapy, the addition of metformin resulted in significant reductions in blood glucose levels.³ HbA_{1c} levels were reduced by 1.6%, and fasting plasma glucose levels dropped 74 mg/dl more in the patients treated with combination metformin/glyburide than in those treated with glyburide alone.³ This initial trial with metformin suggested the efficacy of combination sulfonylurea/metformin therapy.

Another earlier study⁴ that suggested the efficacy of combination metformin/sulfonylurea therapy was carried out in 55 type 2 diabetic patients with a duration of diabetes of <30 years who were all treated with insulin for <10 years. Discontinuation of insulin and reinitiation of oral combination metformin/sulfonylurea therapy were attempted in all patients. Reinitiation of oral therapy was successful in 76% of the patients and was accompanied by a 1.3% reduction ($P = 0.001$) in HbA_{1c} in the patients who experienced successful reinitiation.

These earlier trials carried out when metformin was available only as a singular formulation suggested the power of using combination sulfonylurea/metformin therapy. Therefore, the release of a glyburide/metformin formulation in a single tablet may have important advantages for patients.

Six hundred thirty-nine patients whose diabetes was inadequately con-

IN BRIEF

The pharmacological management of type 2 diabetes has changed dramatically in the past few years with the introduction of many new medications, including α -glucosidase inhibitors, a biguanide, the thiazolidinediones, insulin analogs, meglitinides, and d-phenylalanine derivatives. These new agents have dramatically increased the number of options available to providers and patients. Combination therapy has become commonplace for the management of hyperglycemia in patients with type 2 diabetes. This article briefly reviews some of the more recent pharmacological advances in diabetes care.

trolled with up to half the maximum dose of a sulfonylurea were studied in a 16-week, double-blind, controlled trial. The patients were randomized to receive either glyburide alone, metformin alone, a glyburide 2.5 mg/metformin 500 mg combination, or a glyburide 5 mg/metformin 500 mg combination.

Those who were randomized to either type of monotherapy experienced no significant improvement in glycemic control. Patients in the groups receiving either the glyburide 2.5 mg/metformin 500 mg combination or the glyburide 5 mg/metformin 500 mg combination experienced reductions in HbA_{1c} that were 1.7% greater than those seen with glyburide monotherapy and 1.9% greater than those seen with metformin monotherapy.⁵ These results are summarized in Table 1.

Another trial evaluated 806 patients with type 2 diabetes inadequately controlled with diet and exercise alone. The patients were randomized to receive either placebo (*n* = 147); glyburide monotherapy, 2.5 mg (*n* = 142); metformin monotherapy, 500 mg (*n* = 141); glyburide/metformin, 1.25 mg/250 mg (*n* = 149); or glyburide/metformin, 2.5 mg/500 mg (*n* = 152). Doses of these medications were titrated over an 8-week period up to a maximum of 4 tablets daily based on patients' response to the medication. Final average doses were 5.3 mg for glyburide monotherapy, 1,317 mg for metformin monotherapy, 2.8/557 mg for the low-dose glyburide/metformin therapy, and 4.1/824 mg for

the high-dose glyburide/metformin therapy.

Treatment with the new combination formulation as initial pharmacotherapy resulted in greater improvement of glycemic control.⁵ Reductions in HbA_{1c} concentrations in the combination therapy groups were greater than those seen in either of the monotherapy groups. The low-dose combination group had 0.24 and 0.44% greater reductions than were observed in the glyburide and the metformin monotherapy groups, respectively. In the high-dose combination group, HbA_{1c} concentrations were 0.29 and 0.49% lower than were observed in the glyburide monotherapy group and the metformin monotherapy group, respectively. These results are summarized in Table 2.

Interestingly, it was reported that 66% of patients achieved HbA_{1c} concentrations <7% when they were treated initially with the high-dose glyburide/metformin combination, whereas 61% of the patients taking the low-dose combination were receiving only one or two tablets per day at the end of this study. This study suggested that the low-dose combination formulation is both effective and safe when used initially in the management of type 2 diabetes.

For patients with type 2 diabetes whose hyperglycemia cannot be managed by diet and exercise alone, the recommended starting dose of glyburide/metformin combination therapy is 1.2/250 mg, taken once a day with a meal. In patients whose baseline HbA_{1c}

is >9% or in those with a fasting plasma glucose (FPG) >200 mg/dl, the recommended initial dose of glyburide/metformin therapy is 1.25/250 mg twice daily, taken with the morning and evening meal. Dose titration should occur every 2 weeks until a minimum effective dosage is achieved. Titrations should be made in increments of 1.25/250 mg.

In the above-mentioned clinical trials using the glyburide/metformin combination as initial therapy, there is no experience with total daily doses of >10/2,000 mg daily. For newly diagnosed patients, glyburide/metformin 5/500 mg should not be used initially because of an increased risk of hypoglycemia.

For patients who have previously been treated with glyburide or another sulfonylurea or metformin monotherapy and who still have inadequately controlled blood glucose levels, the recommended starting dose of the glyburide/metformin formulation is 2.5/500 mg or 5/500 mg twice daily. The daily dose should be titrated approximately every 2 weeks in increments of no greater than 5/500 mg until the minimum effective dose is determined or a maximum dose has been reached.

Extended-release metformin

A new extended-release formulation of metformin (Glucophage XR) was recently released. This formulation offers the option of giving the medication as a single daily dose with the largest meal of the day.⁶

A trial evaluating the effects of extended-release metformin evaluated 217 patients with type 2 diabetes who were initially being treated with conventional metformin at a dose of 500 mg twice a day and whose HbA_{1c} concentrations averaged <8.5%. These patients were randomized to continue conventional metformin at the same dose; to receive extended-release metformin, 1,000 mg daily; or to receive extended-release metformin, 1,500 mg daily, for a 24-week period. At 12 weeks, patients whose HbA_{1c} concentration was >8% had their daily dose increased by 500 mg

Table 1. HbA_{1c} reductions resulting from glyburide/metformin combination therapy versus monotherapy with either agent in patients whose diabetes was poorly controlled with sulfonylureas⁵

	HbA _{1c} reduction compared to glyburide monotherapy	HbA _{1c} reduction compared to metformin monotherapy
Glyburide/metformin 2.5/500 mg combination therapy	1.7%	1.9%
Glyburide/metformin 5/500 mg combination therapy	1.7%	1.9%

Table 2. HbA_{1c} reductions resulting from glyburide/metformin combination therapy versus monotherapy with either agent in patients whose diabetes was poorly controlled with diet and exercise alone⁵

	Placebo	Glyburide monotherapy	Metformin monotherapy	Low-dose glyburide/metformin combination therapy	High-dose glyburide/metformin combination therapy
Baseline HbA _{1c} (%)	8.14	8.14	8.23	8.22	8.20
Change from baseline (%)	-0.21	-1.24	-1.03	-1.48	-1.53
Difference from placebo (%)		-1.02	-0.82	-1.26	-1.31
Difference from glyburide monotherapy (%)				-0.24	-0.29
Difference from metformin monotherapy (%)				-0.44	-0.49

in all groups. Baseline mean HbA_{1c} concentrations were similar among the groups.

Patients in all groups experienced slight increases in FPG levels at week 12 and at week 24. The smallest increase in FPG was observed in the group taking extended-release metformin, 1,500 mg. The majority of patients who began the trial with an HbA_{1c} <7% maintained good control at 12 and 24 weeks. While the incidence of adverse events was slightly higher in patients receiving extended-release metformin than in those receiving conventional metformin (86.3 vs. 81.7%), the incidence of gastrointestinal adverse effects was similar between the two groups. The study concluded that at the same total daily dose of metformin, once-daily extended-release metformin provided glycemic control similar to that provided by conventional metformin given twice daily.⁷

Because compliance plays a major role in our ability to treat chronic disease, it seems reasonable to conclude that the simplification of a regimen through the use of an extended-release formulation such as this may be a prudent choice in some cases.

New Secretagogue

As mentioned earlier, it is well documented that type 2 diabetes results from two impairments: a relative insulin deficiency and insulin resistance. With this in mind, it seems logical to utilize an

insulin secretagogue in the early stages of type 2 diabetes, when β -cell function is still viable. Although patients with type 2 diabetes may have high fasting insulin levels, they also have a blunted first-phase insulin response to a glycemic challenge.⁸ This blunting of first-phase insulin release results in prolonged postprandial hyperglycemia. Earlier agents (sulfonylureas), which were utilized to target this defect, increased overall insulin concentrations but often failed to improve first-phase insulin release.

Recently, a new category of compounds, the d-phenylalanine derivatives, has been released to the U.S. market. Nateglinide (Starlix) is the only d-phenylalanine derivative currently available. Although it is similar to the meglitinide compound repaglinide (Prandin), it may offer some distinct advantages to this earlier compound.

A recent study⁹ compared the effects of nateglinide with those of glyburide on post-meal glycemic excursions and insulin secretion in 152 patients with type 2 diabetes. The study found that nateglinide increased early insulin response. Additionally, the overall insulin exposure in glyburide-treated patients was twice that in nateglinide-treated patients.

The study concluded that selectively enhancing early insulin release with nateglinide provided excellent mealtime glucose control while minimizing total

insulin exposure. This suggests that nateglinide causes a greater trend toward the normalization of early-phase insulin response than does the sulfonylurea glyburide.

Another trial¹⁰ of 15 healthy volunteers compared the effects of 120 mg of nateglinide to those of 0.5 mg repaglinide, 2 mg of repaglinide, and placebo. Patients received each dose only one time, and each dose was separated by 48 h. Pharmacokinetic and pharmacodynamic assessments were carried out from time zero to 12 h post-dose.

Nateglinide was associated with a more rapid induction of insulin secretion than either 2 mg repaglinide, 0.5 mg repaglinide, or placebo. When doses of trial medication were given 10 min before meals, insulin concentrations decreased rapidly in nateglinide-treated patients and were similar to those of placebo-treated patients within 2 h after the dose. Conversely, peak insulin concentrations were delayed in patients receiving 2 mg of repaglinide and returned to baseline more slowly than in those receiving nateglinide. Nateglinide treatment resulted in a statistically significant lower average plasma glucose concentration in the interval from time zero to 2-h post-dose than did either dose of repaglinide or placebo. Additionally, glucose concentrations returned more rapidly to baseline levels with nateglinide than with either dose of repaglinide. The hypoglycemic effect of

repaglinide continued up to 6 h after the dose.

The study concluded that, in nondiabetic volunteers, nateglinide produced a more rapid and short-lived stimulation of insulin secretion than did repaglinide and resulted in lower postprandial glucose excursions.

Another study¹¹ evaluated the efficacy and tolerability of nateglinide when used in combination with metformin and also compared monotherapeutic nateglinide to monotherapeutic metformin. This was a randomized, double-blind trial in which patients underwent a 4-week placebo run-in followed by 24 weeks of therapy with either 120 mg of nateglinide before meals, 500 mg of metformin three times daily, combination metformin/nateglinide, or placebo. HbA_{1c} concentrations and FPG levels were evaluated. A Sustacal challenge was administered at weeks 0, 12, and 24.

At the end of the study, average HbA_{1c} concentrations were reduced from baseline with both nateglinide and metformin, whereas those receiving placebo experienced an increase in HbA_{1c} (-0.5, -0.8, and +0.5%, respectively). Changes in FPG followed a similar trend. Combination therapy resulted in a reduction in HbA_{1c} levels 1.4% greater than that from monotherapy. A greater reduction in mealtime glucose was noted in the nateglinide monotherapy group after a Sustacal challenge than in those receiving either metformin monotherapy or placebo. Patients treated with combination therapy experienced an even greater reduction in mealtime glucose excursions than did those receiving monotherapy.

The study concluded that nateglinide caused a reduction in mealtime glucose excursions, whereas metformin primarily affected FPG concentrations. The study also concluded that the combination of nateglinide and metformin was complementary and resulted in improved HbA_{1c} concentrations, FPG levels, and postprandial hyperglycemia.

Nateglinide and repaglinide are structurally only distantly related, but

their clinical effects are frequently compared. Nateglinide was reported to cause hypoglycemia in 2.4% of patients in phase III trials compared to 31% of patients treated with repaglinide.^{12,13} Nateglinide does not normally require titration, whereas repaglinide does. The area under the curve (AUC) of repaglinide is increased more than fourfold in patients with severe renal impairment, whereas the AUC of nateglinide is unchanged in this population.^{12,13} Although there have not yet been any direct head-to-head clinical trials comparing these two compounds in a diabetic population, available data suggest that nateglinide may offer perquisites not found with repaglinide.

Nateglinide is a new oral secretagogue that has a very rapid and short-lived effect. It does not normally require titration, nor does it require dosage adjustments in the elderly, in patients with mild to severe renal insufficiency, or in patients with mild hepatic insufficiency. No major significant drug interactions have been identified to date. This medication is useful as monotherapy in newly diagnosed or previously drug-naïve patients. It is also useful in combination with non-secretagogue medications.¹²

Glimepiride Findings

Recent data have suggested that the second-generation sulfonylurea glimepiride (Amaryl) may be associated with a lower incidence of hypoglycemia and less weight gain and may improve insulin sensitivity compared to other sulfonylureas. These findings are significant enough to warrant further investigation.

The frequency of severe hypoglycemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide (a European formulation) was compared in a population-based study from 1997 to 1999 in an area with 200,000 inhabitants.¹⁴ Severe hypoglycemia was defined as the need for intravenous glucose injection or glucagon. Blood glucose values in 21,607 patients who were seen in the

emergency department of the region's hospital were measured in the laboratory. Additionally, 5,104 patients who were seen by emergency medical personnel in the field were tested with a rapid blood glucose test.

The study found that, although glimepiride was used only 8% less than glibenclamide (4,660 vs. 5,531 patient-years) it was associated with considerably less hypoglycemia. Of the 201 cases of severe hypoglycemia, 32 were caused by glibenclamide, whereas only 2 were caused by glimepiride. One episode was reported in a patient treated with a combination of these two products. The incidence of severe hypoglycemia was 5.8/1,000 patient-years for glibenclamide and 0.43/1,000 patient-years in those treated with glimepiride.

The study concluded that, under conditions of everyday practice, glimepiride caused significantly fewer episodes of severe hypoglycemia than did glibenclamide. The tenfold difference in hypoglycemia is striking and warrants further investigation.

A recent meta-analysis of the long-term treatment of patients with type 2 diabetes¹⁵ evaluated the effects of glimepiride on weight gain. The study reviewed published literature and internal databases and included two U.S. and two multinational clinical trials that were double-blind, randomized, actively controlled, and 12 months in duration. Weight or body mass index was measured baseline, 6 months, and 12 months. Four trials included 14,044 patients treated with glimepiride who had valid baseline and 12-month weight measurements. The mean age of these patients was 60.7 years.

The observed mean \pm standard deviation for the change in weight from baseline to 12 months for the glimepiride-treated patients was 0.0 ± 3.4 kg. The 95% confidence interval for the mean change was 0.16–0.21 kg and revealed no statistically significant change in weight ($P = 0.81$).

The study concluded that long-term treatment with glimepiride in patients

with type 2 diabetes causes no significant change in weight.¹⁵ Although this was a meta-analysis and as such must be viewed with appropriate caution, it does suggest a difference in the effect on weight imparted by glimepiride versus the weight gain usually encountered with sulfonylureas. As with the previously mentioned study, this warrants further investigation.

Glimepiride's effect on peripheral sensitivity was evaluated in 10 healthy, glucose-tolerant, and insulin-resistant children of patients with type 2 diabetes.¹⁶ These subjects were tested in a placebo controlled, double-blind, crossover study. Patients received either intravenous saline or lyophilized glimepiride in a randomized order on two different testing occasions. A three-step hyperinsulinemic euglycemic glucose clamp study was performed on both occasions to determine insulin sensitivity. Glimepiride-induced insulin secretion was inhibited by the use of somatostatin. Insulin sensitivity was compared using a two-sided paired t-test.

Plasma glucose and insulin concentrations were similar during the glimepiride and the saline infusion studies. Insulin sensitivity without glimepiride was significantly lower in the first two steps of the hyperinsulinemic euglycemic clamp studies.

This study concluded that glimepiride infusion increases peripheral insulin sensitivity under mild to moderate hyperinsulinemic conditions.¹⁶ Although this was a small study involving nondiabetic patients, its findings are consistent with other trials that have suggested that glimepiride offers an insulin-sparing activity. Previous studies have suggested that glimepiride stimulates glucose uptake and utilization by translocation of the glucose transporter protein GLUT4 in fat and muscle cells.¹⁷ Previous studies have also suggested that glimepiride is associated with significantly lower fasting plasma insulin and C-peptide concentrations than is glyburide.¹⁷ These findings all suggest that glimepiride may be associated with an insulin-sparing

activity.

Further work in this area will be important because other second-generation sulfonylureas are available generically and may offer a significant cost savings over glimepiride. Although these other sulfonylureas may offer a short-term cost savings, glimepiride may turn out to be the least expensive and the safest of the sulfonylurea agents if indeed it is associated with less weight gain, is insulin-sparing, and causes less hypoglycemia. Conversely, if these findings are artifact, then the use of the generic agents may be warranted.

New Insulins

In the past few months, two new insulin analogs have been introduced to the market. Insulin glargine (Lantus) is a long-acting insulin analog, and insulin aspart (Novolog) is a short-acting product. Both will be useful in some cases of type 2 diabetes.

Glargine

In the past, short-acting insulin preparations have been used with great success to control postprandial glycemic excursions. However, the search for an insulin that can mimic normal basal insulin secretion continued until recently. Earlier long-acting and intermediate-acting insulins have pharmacokinetic profiles that make them difficult to use and do not mimic normal basal insulin secretion. An ideal basal insulin would be absorbed slowly, provide a relatively constant plasma concentration, have no peak, have consistent bioavailability, and exhibit a long half-life, which would lend itself to once-daily administration. Such a product has been realized with the introduction of glargine.

Glargine is a human insulin analog produced by recombinant DNA technology via nonpathogenic *E. coli* bacteria. This insulin is soluble at a pH of 4 but has a relatively slow solubility when injected into a neutral pH environment. After glargine is injected, microparticles form, and the insulin is resolubilized and absorbed slowly. This provides

a relatively constant level of insulin with no discernable peaks over a 24-h period.

Glargine differs from human insulin by the addition of two arginines to the C terminus of the B chain and with the substitution of glycine for asparagine at position A21.¹⁸ This molecule is as potent as human insulin. Glargine is formulated as a clear aqueous solution of 100 units/ml.

A study of 518 patients with type 2 diabetes¹⁹ evaluated the efficacy and safety of insulin glargine over a 28-week period. Patients who were previously treated with insulin were randomized to receive either glargine once daily or NPH once or twice daily. Doses of insulin were adjusted to obtain fasting glucose levels of <6.7 mmol/l.

Both treatment groups showed similar reductions in HbA_{1c} concentrations. The difference in mean change from baseline to endpoint was not statistically significant between the glargine group and the NPH group. Similarly, the treatments were associated with comparable reductions in fasting glucose levels. The incidence of mild symptomatic hypoglycemia was similar in the glargine and the NPH groups. A statistically significant 25% reduction in nocturnal hypoglycemia was observed in the glargine group. Additionally, patients in the glargine group experienced significantly less weight gain than did those in the NPH group (0.4 vs. 1.4 kg).

This study concluded that glargine given once daily is as effective for glycemic control as one or two injections of NPH. The study also concluded that patients treated with glargine experienced less nocturnal hypoglycemia and less weight gain than those treated with NPH.

This new basal insulin analog offers a reasonable alternative to other long-acting or intermediate-acting insulins for patients previously treated with oral agents. It also offers a reasonable alternative to patients using one or two injections of NPH, either in combination with oral agents or in combination with rapid-acting insulins.

Aspart

The FDA recently approved this second short-acting insulin analog.²⁰ Aspart is homologous to human insulin except for the substitution of aspartic acid for proline at B28.^{20–22} This substitution reduces the formation of dimers and hexamers, thus promoting the retention of the insulin molecule in the monomeric form. This results in an ultra-short-acting analog.

In a study comparing the pharmacokinetics of aspart to those of regular human insulin, the time to reach maximum concentration was significantly less with aspart than with regular human insulin (52 vs. 145 min, respectively).²³ The concentration maximum was twice as high with aspart as with regular insulin. The mean residence time was significantly less with aspart than with regular insulin (149 vs. 219 min, respectively). Finally, the time to reach minimum blood glucose concentrations after injection was significantly lower with aspart than with regular insulin (94 vs. 226 min, respectively).

Aspart was compared to regular insulin in a trial evaluating 884 patients with type 2 diabetes.²⁴ These patients received either aspart or regular insulin for 6 months. Investigators reported a statistically insignificant improvement in HbA_{1c} levels at 6 months (7.8 vs. 7.9%, respectively). However, in an extension of this trial,²⁴ investigators reported significantly less nighttime hypoglycemia with aspart than with regular insulin (16 vs. 34%, respectively).

One study²⁵ reported the effects of mixed NPH and aspart with separate injections of NPH and aspart. No differences were reported between these two regimens. Thus, it appears that aspart may mixed with NPH without altering the time-action profiles of either insulin.

The ability to mix these insulins will make the use of split and mixed regimens more acceptable to patients. It should be noted, however, that no studies have been carried out evaluating the pharmacokinetic and pharmacodynamic

effects of mixing aspart with lente or ultralente insulin.²⁰

In summary, aspart offers an alternative to the use of lispro. It displays similar pharmacokinetic and pharmacodynamic characteristics and controls postprandial hyperglycemia to a similar extent as does lispro.

Summary

The past few years have brought several new products to market that are useful in the management of type 2 diabetes. The glyburide/metformin combination and the extended-release metformin formulation may be useful for many patients because of their ease of compliance. The introduction of the glyburide/metformin combination also brings into focus the importance of treating type 2 diabetes as a dual-defect disease.

The new insulin secretagogue nateglinide is an oral medication that essentially normalizes first-phase insulin response, thus controlling postprandial hyperglycemic excursions without causing a high rate of hypoglycemia. Recent data have also demonstrated that glimepiride may offer some distinct advantages over the other sulfonylureas.

Finally, two new insulin products, aspart and glargine, offer distinct characteristics that will make them optimal choices in certain situations. Aspart, a rapid-acting analog, is useful in controlling postprandial hyperglycemic excursions, whereas glargine offers the first true basal analog. A single injection of glargine provides continuous infusion of insulin into the bloodstream for a 24-h period.

Thus, after a long period of relative stability in treatment choices for type 2 diabetes, practitioners now have a wealth of new options, allowing them to tailor treatment regimens for their type 2 diabetic patients to address a wide range of circumstances and situations.

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