Glucose homeostasis is regulated by a complex interplay of multiple hormones, including hormones from the pancreas (insulin, glucagon, and amylin) and the gut (glucagon-like peptide 1 [GLP-1] and glucose-dependent insulinotropic polypeptide). Most therapeutic options are focused on abnormal insulin secretion and signalling and do not address the role these other hormones play in glucose regulation and the diabetic state.

The inability to control glycemia over the long term utilizing single oral agents is reflected by the need to use various agents, alone or in combination, over time. In addition, the presence of associated side effects and clinical shortcomings of many therapies has prompted the search for new therapeutic agents that address the underlying dysregulation of multiple hormones found in people with diabetes. One of these agents, exenatide, mimics several of the actions of GLP-1 and is the first agent in a new class called incretin mimetics.

Exenatide was approved by the Food and Drug Administration in 2005 as an adjunctive therapy to metformin and/or sulfonylurea regimens for individuals with type 2 diabetes who have not achieved adequate glycemic control. Clinical trials indicate that subjects taking 10 μg of exenatide twice daily for 6 months had hemoglobin A1c (A1C) reductions of ~1% and body weight reductions of ~2 kg. After 1.5 years of exenatide treatment, reductions in A1C were sustained (1.1%), and body weight reductions were progressive (4.4 kg). In addition, exenatide treatment for 1.5 years resulted in improvements in some cardiovascular risk factors. For individuals with type 2 diabetes not achieving adequate glucose control with metformin and/or sulfonylureas, incretin mimetics such as exenatide may offer the opportunity for improved glycemic control with fewer clinical shortcomings than other available treatments.

Both GLP-1 and GIP are secreted by the gut in response to oral nutrient intake and neuronal signals. GLP-1 and GIP are termed “incretins” because they mediate the incretin effect. The incretin effect is apparent when glucose delivered orally to achieve plasma glucose concentrations equivalent to intravenously administered glucose elicits a greater insulin secretory response than that seen with intravenous glucose.

Glucose enters the circulation through postprandial intestinal absorption and hepatic release (glycogenolysis and gluconeogenesis), both of which are abnormally regulated in type 2 diabetes. The appearance of glucose is also influenced by the rate of gastric emptying, which determines the rate of intestinal absorption and can be paradoxically accelerated.
in people with type 2 diabetes when compared with nondiabetic control subjects. The liver’s contributions to postprandial hyperglycemia, glycogenolysis, and gluconeogenesis are under the control of glucagon. In individuals without diabetes, glucagon stimulates hepatic glucose production during the fasting state to maintain euglycemia. After meals, when hepatic glucose production is no longer needed, glucagon concentrations rapidly decline. In people with diabetes, glucagon concentrations remain elevated or even paradoxically increase, contributing further to postprandial hyperglycemia.

Postprandial hyperglycemia is an important contributor to elevated hemoglobin A1C (A1C), especially when the A1C is between 7 and 9%. Recent studies suggest that postprandial hyperglycemia may be a better predictor of cardiovascular risk than fasting glycaemia or A1C.

The postprandial rise in glucose is modulated by both GLP-1 and amylin. GLP-1 is reduced in type 2 diabetes, whereas amylin is deficient in type 1 diabetes and impaired in type 2 diabetes. These hormones regulate the rate of glucose appearance in the circulation through regulation of gastric emptying, suppression of inappropriate postprandial glucagon secretion, and moderation of food intake. In addition, GLP-1, but not amylin, helps reduce postprandial glucose excursions by enhancing glucose-dependent insulin secretion. Interestingly, despite an exaggerated GIP response to glucose ingestion, people with type 2 diabetes have features of GIP resistance. Thus, GIP is not a promising therapeutic candidate. Therefore, research on incretins has centered on restoring or enhancing GLP-1–like glucoregulatory effects.

Maintenance of glucose homeostasis requires a complex interplay of insulin, glucagon, amylin, and incretin hormones such as GLP-1. In type 2 diabetes, relative deficiencies of insulin, amylin, and GLP-1, combined with glucagon excess and accelerated gastric emptying, result in an imbalance between the rate of glucose appearance and disappearance, which manifests clinically as hyperglycemia.

Therapeutic agents have been or are currently being developed that share similar glucoregulatory actions as GLP-1. Two general approaches are being pursued to increase GLP-1–like activity in diabetes: agents that block degradation of endogenous GLP-1 by inhibiting dipeptidyl peptidase-IV (DPP-IV), an enzyme that cleaves GLP-1 (DPP-IV inhibitors). Although several agents in both classes are in development, including liraglutide (NN2211), an incretin mimetic, and vildagliptin (LAF237) and sitagliptin (MK-0341), both DPP-IV inhibitors, thus far, the only agent approved by the U.S. Food and Drug Administration for use in the treatment of diabetes is exenatide.

Exenatide is the synthetic version of exendin-4, a naturally occurring 39–amino acid peptide hormone originally isolated from Gila monster salivary glands, with several glucoregulatory actions similar to GLP-1. Exenatide enhances glucose–dependent insulin secretion, suppresses inappropriately elevated postprandial glucagon secretion, slows gastric emptying, and reduces food intake. Importantly, exenatide has also been shown to restore the acute responsiveness of the β-cell to secrete insulin.

**TREATMENT OPTIONS FOR PATIENTS WITH TYPE 2 DIABETES**

Commonly used pharmacotherapies for people with type 2 diabetes include oral agents that 1) counter insulin resistance (thiazolidinediones [TZDs] and biguanides [metformin], 2) promote insulin secretion (sulfonylureas, meglitinides, and d-phenylalanine derivatives), 3) reduce hepatic glucose production (biguanides and TZDs), and 4) modulate glucose absorption (α-glucosidase inhibitors) (Table 1). These classes of oral therapies, when combined with behavioral lifestyle changes, can effectively improve glucose homeostasis in the short term. However, although initial treatment often yields a significant decrease in A1C, these therapies have not been shown to halt the progressive decline in β-cell mass and function. Over time, these agents may become less effective, even in patients who initially responded. Many of the available treatments affect either insulin secretion or insulin resistance. However, replication of the endogenous pattern of insulin secretion, suppression of postprandial glucagon secretion, and modulation of the abnormally rapid gastric emptying that characterizes diabetes have not been addressed previously. Recently discovered abnormalities of the gut and pancreatic hormones common to individuals with type 2 diabetes have explained why achieving and maintaining optimal glycemic control is difficult.

Daily postprandial glucose excursions are not well controlled, and 24-hour glucose concentrations fluctuate widely, resulting in either hyperglycemia, hypoglycemia, or both for individuals with diabetes. The continued maintenance of A1C levels markedly above target levels, as reported by epidemiological studies, reaffirms the global challenge in managing diabetes.

When managing any illness, including diabetes, the therapeutic efficacy of any treatment must be balanced with the associated side effect profile and clinical shortcomings because these can influence the achievement of optimal control and individual compliance. Hypoglycemia is a clinical shortcoming that occurs primarily with insulin and sulfonylurea therapy because these agents are not able to completely mimic the physiological patterns of insulin secretion.

Additionally, weight gain appears inseparable from many diabetes therapies, specifically insulin, sulfonylureas, and TZDs, with an estimated 2-kg weight gain for every 1% decrease in A1C. Causes of associated weight gain may include compensatory eating to avoid and treat hypoglycemia, decreased glucosuria, decreased basal metabolic rate, changes in adipose tissue, and fluid retention. This can be particularly frustrating for patients who are already overweight, despite making the recommended lifestyle changes to facilitate weight control.

The weight gain accompanying diabetes treatments is an important health issue because of the strong relationship between obesity and cardiovascular risk factors, such as dyslipidemia and hypertension. Other obesity-related health concerns include an increase in malignancies, cerebrovascular disease, sleep apnea, osteoarthritis, and cholelithiasis.
Additionally, obesity exacerbates hyperglycemia, hyperinsulinemia, insulin resistance, and glucose intolerance, contributing to the development of diabetes. By itself, obesity is an independent risk factor for cardiovascular disease, which accounts for up to 65% of deaths in people with diabetes. This increased cardiovascular risk is in addition to the inherent increased risk from hyperglycemia. In the U.K. Prospective Diabetes Study, each 1% reduction in A1C was associated with a risk reduction of 14% for myocardial infarction and 11% for coronary artery disease. This increased cardiovascu-
lar disease, which accounts for up to 65% of deaths in people with diabetes, is independent of the other factors.

The most common adverse event was mild-to-moderate nausea, which occurred predominantly at the initiation of therapy. Hypoglycemia, the second most common side effect, was almost exclusively mild to moderate in intensity and occurred more often when exenatide was used concomitantly with a sulfonylurea than when exenatide was used with metformin. In fact, when exenatide was used with metformin, hypoglycemia incidence was similar to that seen with metformin alone.

Open-label extension studies of these 30-week trials found that the clinical effects of exenatide on A1C and weight were sustained over time. Patients receiving 10 µg of exenatide twice daily for 82 weeks (30 weeks in the placebo-controlled trials and 52 weeks in open-label extension studies) had sustained reductions from baseline in A1C (−1.1%) and progressive reductions from baseline in body weight (−4.4 kg), with an adverse event profile similar to that seen in the placebo-controlled trials.

Further analysis of the 82-week cohort revealed statistically significant changes from baseline for diastolic blood pressure (−2.7 mmHg), HDL cholesterol (−4.6 mg/dl), and triglycerides (−39 mg/dl). Changes for other parameters, such as systolic blood pressure (−1.3 mmHg), LDL cholesterol (−1.6 mg/dl), and total cholesterol (−2.4 mg/dl), were not statistically significant. The beneficial changes were even more pronounced in the quartile of patients with the largest weight reductions (mean −11.9 kg): diastolic blood pressure −4.4 mmHg, HDL cholesterol +7.3 mg/dl, and triglycerides −93 mg/dl.

Important Considerations
Exenatide has been approved as an adjunctive therapy to metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea to improve glycemic control in patients with type 2 diabetes who have not achieved adequate glycemic control. Exenatide is administered as a subcu-

Table 1. Glucoregulatory Effects (Direct and Indirect) of Various Antidiabetic Agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>↓ Food Intake</th>
<th>Delay Gastric Emptying</th>
<th>Delay Glucose Absorption</th>
<th>↑ Insulin Secretion</th>
<th>↓ Hepatic Glucose Production</th>
<th>↑ Glucose Uptake</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
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<td></td>
<td></td>
<td>Hypoglycemia, weight gain, edema</td>
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<tr>
<td>Insulin secretogogues</td>
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<td></td>
<td></td>
<td>Hypoglycemia, weight gain</td>
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<tr>
<td>Biguanides</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea, nausea, vomiting, bloating</td>
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<tr>
<td>α-glucosidase inhibitors</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea, flatulence</td>
</tr>
<tr>
<td>TZDs</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight gain, edema</td>
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<tr>
<td>Pramlintide*</td>
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<td></td>
<td></td>
<td>Nausea, ↑ insulin-induced hypoglycemia</td>
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<tr>
<td>Exenatide</td>
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<td></td>
<td></td>
<td></td>
<td>Nausea, sulfonylurea-induced hypoglycemia</td>
</tr>
</tbody>
</table>

* Synthetic form of amylin

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Is the patient taking insulin or other antidiabetic agents other than a sulfonylurea and/or metformin?

Exenatide is not a substitute for insulin in insulin-requiring patients and should not be used in patients with type 1 diabetes. Abrupt discontinuation of insulin treatment when initiating exenatide may result in hyperglycemia and thus may carry the same risks incurred when any patient who requires insulin to control diabetes stops taking insulin. Exenatide is not to be used in the treatment of diabetic ketoacidosis. The risk of hypoglycemia when exenatide is used with insulin is unknown. Additionally, concurrent use of exenatide with D-phénylalanine derivatives, meglitinides, or α-glucosidase inhibitors has not been studied. Studies of the use of exenatide with TZDs are ongoing.

Is the patient taking a sulfonylurea?

In 30-week placebo-controlled trials, the incidence of hypoglycemia was greater in exenatide-treated patients who were taking a sulfonylurea compared with placebo-treated patients taking a sulfonylurea. However, there was no increased risk of hypoglycemia when exenatide was used with metformin. To reduce the risk of hypoglycemia associated with the use of exenatide and a sulfonylurea, reducing the dose of the sulfonylurea may be considered.

Patients should be informed that they may experience nausea at the beginning of treatment.

Based on the clinical trials, mild to moderate nausea generally occurs within the first days of treatment or with a dose increase. After a month of therapy at 5 μg twice daily, the dose is increased to 10 μg twice daily based on patient tolerability. If significant nausea is experienced with the twice-daily 10-μg dose, patients should reduce their twice-daily dose to 5 μg and then attempt to increase the dose to 10 μg twice daily at a later time.

Antiemetic agents or nonprescription remedies, such as Emetrol or Pepto-Bismol, may help patients with nausea. Additionally, varying the time when exenatide is administered, as long as it is within 1 hour before eating, may be helpful. If significant nausea persists, discontinuation of therapy should be considered.

What other medications is the patient taking?

Exenatide slows gastric emptying and may reduce the absorption of orally administered drugs. Consequently, exenatide should be used with caution in patients receiving oral medications that require rapid gastrointestinal (GI) absorption. For oral medications that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those drugs at least 1 hour before the exenatide injection. If oral medications must be administered with food, patients should be advised to take them with a meal or snack when exenatide is not administered.

Does the patient eat a small breakfast or no breakfast at all?

As long as patients eat something that contains calories for breakfast, they can still take exenatide before breakfast. There are no specific caloric guidelines for exenatide. Patients who do not eat breakfast should take their first exenatide injection before either a morning snack or lunch and their second exenatide injection before dinner, as long as the two injections are at least 6 hours apart.

Does the patient seem reluctant to take exenatide because of the injections?

The profound resistance to injections often seen in patients with type 2 diabetes may be related to the broader negative attitude towards insulin use rather than to the injections themselves. Many of the reasons why patients are reluctant to take insulin injections, such as feelings of personal failure, perceptions of loss of control of their lives, and perceptions of complexity of insulin regimens and increasing disease severity, may not apply to exenatide. The availability of exenatide in a pen device may ease some of the injection concerns (i.e., complexity, convenience). The fixed-dose nature of exenatide also simplifies treatment and may ease fears that inappropriate dosing will lead to hypoglycemia, as can occur with insulin. In severe cases of needle phobia, cognitive behavioral therapy has been shown to be of value.

Does the patient have renal disease or severe GI disease?

Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min). Single doses of 5 μg exenatide were not well-tolerated in this patient population because of GI side effects.

The use of exenatide was associated with GI side effects in the registration trials, including nausea (44 vs. 18% with placebo), vomiting (13 vs. 4% with placebo), diarrhea (13 vs. 6% with placebo), and dyspepsia (6 vs. 3% with placebo). Exenatide is not recommended in patients with severe GI disease, including gastroparesis.

CASE STUDIES

Joyce

Joyce is a 58-year-old Hispanic woman who was diagnosed with type 2 diabetes 8 years ago. After diagnosis, Joyce tried diet and exercise for 2 years but was never able to reach her goal. She then tried the sulfonylurea glyburide, which worked fairly well for a time. (Her A1C dropped from 9.5 to 7.2%). Two years later, metformin was added, and her A1C dropped to 6.8%. However, 4 years after adding metformin, her A1C rose to 8.1%.

Joyce attributes this loss of diabetes control to competing demands in her life. She has no time to exercise because she is taking care of an elderly parent. Joyce has been struggling with her weight for several years. She had been avoiding follow-up clinic visits because she did not want to take insulin, in part because of the possible weight gain. However, Joyce is willing to try exenatide.

Medical history

In addition to diabetes, Joyce has dyslipidemia, hypertension, hypothyroidism, and obesity. Her diabetes medications include glipizide ER, 10 mg twice daily, and metformin, 1,000 mg twice daily. Other medications include premarin, lisinopril/hydrochlorothiazide, and synthroid.

Course of treatment

Joyce started 5 μg of exenatide twice daily. Despite “feeling pregnant” because of nausea after 2 weeks of treatment, she was emphatic that she did not want to stop exenatide treatment. After 4 weeks of treatment, the nausea had ceased, and her dose was increased to 10 μg exenatide twice...
daily. She experienced nausea and vomiting during the 1st week on the higher dose, so her dose was decreased back to 5 μg twice daily for 1 month. Subsequently, her dose was increased again to 10 μg twice daily, and she experienced no further nausea.

Joyce’s morning glipizide was discontinued to minimize the risk of hypoglycemia. However, her fasting glucose concentrations remained high, so the morning glipizide dose was later reinstated. She reported no symptoms of hypoglycemia.

During the 4 months of her treatment with exenatide, Joyce saw improvements in her triglycerides and LDL cholesterol concentrations. She is very happy with her improved glucose control and says she feels better and has more energy.

Outcomes

When Joyce first started exenatide on May 1, her A1C was 8.1%, her weight was 195 lb, triglycerides were 287 mg/dl, LDL cholesterol was 138 mg/dl, and HDL cholesterol was 32 mg/dl. Four months later, her A1C was 6.7%, her weight was 184 lb, triglycerides were 176 mg/dl, LDL cholesterol was 112 mg/dl, and HDL cholesterol was 33 mg/dl.

Mary

Mary is a 63-year-old white woman diagnosed with type 2 diabetes 4 years ago. At that time, Mary began treatment with metformin and received instruction on medical nutritional therapy and exercise. Using these tools, she maintained her A1C < 6.5% until recently. Over the past year, her A1C increased from 6.2 to 7.2%, and her weight increased from 203 to 213 lb. Next-step treatment options included a TZD or exenatide. Mary chose exenatide in an effort to prevent further weight gain. Once reassured that exenatide was not insulin, she seemed unconcerned that exenatide was given by injection.

Medical history

In addition to diabetes, Mary has dyslipidemia, hypertension, and obesity. For diabetes, she takes metformin, 1,000 mg twice daily. Her other medications include lisinopril, hydrochlorothiazide, losartan, amlodipine, and simvastatin.

Course of treatment

Mary started 5 μg exenatide twice daily in August. She reported a decrease in her appetite and a sense of fullness early in her meals. She experienced no tolerability issues, so after 1 month, Mary’s dose was increased to 10 μg twice daily. The effects on appetite and satiety persisted. After 4 months of treatment with exenatide, both her A1C and weight had decreased. She was very pleased with her progress and felt the effort required to manage her diabetes was very manageable.

Outcomes

When she started exenatide, Mary’s A1C was 7.2%, and her weight was 213 lb. After 4 months, her A1C was 6.4%, and her weight was 202 lb.

Key Clinical Points From These Cases

- For patients currently on twice-daily sulfonylurea therapy, consider discontinuing the morning dose of sulfonylurea. If the patient does not experience hypoglycemia and fasting glucose is high, consider reinstating the morning dose of sulfonylurea.
- Nausea associated with exenatide use is generally self-limiting and mild to moderate in intensity. Many patients are willing to tolerate a degree of nausea because they otherwise feel better and are losing weight. Patients may find they need to balance the inconvenience of nausea with the clinical benefits of glycemic control and weight reduction.
- Many patients with diabetes have other cardiovascular risk factors, such as obesity, hypertension, and dyslipidemia. The concomitant decrease in weight and triglycerides seen with exenatide treatment provides a potential additional health benefit for these patients.
- Patients are willing to use an injectable medication, especially if they feel it may provide benefit. It is important to emphasize that exenatide is not insulin and thus does not carry some of the burdens of insulin injection therapy. Of course, it must also be stressed for those patients already taking insulin that exenatide is not a replacement for insulin.
- For injection-naive patients and especially for those who are fearful of injections, it is helpful to demonstrate exenatide injection technique and have patients give themselves an injection before leaving the office or clinic.
- Many patients report symptoms along the continuum from fullness to nausea. When nausea occurs, it is often of short duration and generally does not lead to discontinuation of exenatide.

CONCLUSIONS

Diabetes is increasingly recognized as a disease affecting multiple organs and hormones. As a result, many new therapies are being developed that address imbalances beyond insulin resistance and defective insulin secretion. Exenatide, an incretin mimetic, is an approved therapeutic agent that shares several glucoregulatory activities with GLP-1, a naturally occurring gastrointestinal hormone dysregulated in diabetes.

For people with type 2 diabetes who are not able to achieve adequate glycemic control with metformin and/or a sulfonylurea, exenatide offers several potential therapeutic benefits. Specifically, adding exenatide treatment results in sustained reduction in A1C and progressive reduction in body weight, with reductions in these parameters effective to at least 1.5 years. Additionally, treatment with exenatide for 1.5 years is associated with improvements in cardiovascular risk factors, such as diastolic blood pressure, triglycerides, and HDL cholesterol.

A thorough understanding of patients’ medical history and lifestyle preferences is critical when initiating any new therapy. Exenatide is not a substitute for insulin and is not indicated for treatment of type 1 diabetes or diabetic ketoacidosis.

Individuals currently taking a sulfonylurea may need to reduce the sulfonylurea dose to minimize the risk of hypoglycemia. For most patients, nausea at initiation of therapy is transient and does not lead to discontinuation of exenatide. Patients who have severe renal or GI disease should not take exenatide. With these caveats in mind, adding exenatide offers a unique therapeutic option for many patients with type 2 diabetes who are unable to achieve desired glycemic control with metformin, sulfonylureas, or a combination of these two oral agents.
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References

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Note of disclosure: Dr. Hood has received honoraria for speaking engagements and has served on an advisory board for Amylin Pharmaceuticals and Eli Lilly and Co. Ms. Valentine has served on an advisory board and received honoraria from Amylin and Eli Lilly. Dr. Mac is an employee of and stock shareholder in Amylin. Dr. Polonsky has served as a paid consultant and advisory board member for Amylin. These companies have collaborated on the manufacturing and marketing of exenatide.