

Lixisenatide: A New Member of the Glucagon-Like Peptide 1 Receptor Agonist Class of Incretin Therapies

Charles F. Shaefer, Jr.

■ IN BRIEF In the past decade, various incretin-based therapies have emerged in clinical practice. These drugs, including dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists lower A1C with weight-neutral or weight-lowering effects and a relatively lower risk of hypoglycemia. This article provides a review of lixisenatide, a once-daily GLP-1 receptor agonist for the treatment of type 2 diabetes.

Lixisenatide is a once-daily (QD), fixed-dose glucagon-like peptide 1 (GLP-1) receptor agonist. As an antidiabetic drug that is associated with a minimal risk of hypoglycemia and little likelihood of weight gain (weight loss is usually reported), lixisenatide has great potential, especially for use by primary care providers (PCPs) who fear treatment-associated complications and embrace easily delivered and well-tolerated therapies. Lixisenatide possesses properties that set it apart from other GLP-1 receptor agonists and make it especially suitable for prandial use.

The Incretin System

Knowledge of the incretin system began to emerge in 1902, when Bayless and Starling discovered secretin, which arose from the gut after food ingestion and caused a pancreatic endocrine response that affected disposal of carbohydrates (1). Gut extracts were first used as a chemical excitant to treat diabetes in 1906 (2). Several decades later, Zunz and La Barre prepared an intestinal extract that could cause glucose lowering in dogs, and La Barre coined the term “incretin” to describe this humoral activity of the gut that might enhance endocrine secretion from the pancreas (3,4). However, af-

ter this initial flurry of successful work, subsequent experiments conducted with intestinal extracts failed to lower glucose in fasting dogs (5).

Although these experiments were likely the first hint of the glucose-dependent aspect of insulin release from the pancreatic β -cell under the influence of gut hormones, these unexpected findings were not appreciated, and thus, interest in incretin therapy failed to progress. Incretin research lay fallow until the early 1960s, when Yalow and Berson developed a radioimmunoassay for endogenous insulin in man (6). It only took a few years to determine that ~50% of circulating insulin was stimulated by glucose passing through the gut (7).

These findings revived interest in the incretin system, and, in the late 1970s, Creutzfeldt proposed a definition of incretins that is still accepted today: substances that are released by nutrients passing through the gut, especially carbohydrates, that stimulate insulin secretion at physiologic levels in the presence of elevated blood glucose concentrations (8). Soon, the incretin system emerged as a valid therapeutic target for the management of diabetes, which led

University Health Systems—Primary Care and Medical College of Georgia, Augusta University, Augusta, GA

Corresponding author: Charles F. Shaefer, Jr., cshaefer@uh.org

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TABLE 1. Differential Effects of GLP-1 Receptor Agonists

	GLP-1 Receptor Agonists	
	Short-Acting	Long-Acting
Compounds	Exenatide	Albiglutide
	Lixisenatide	Dulaglutide
		Exenatide QW
		Liraglutide
Half-Life	2–5 hours	12 hours to several days
Effects		
Fasting blood glucose	Modest reduction	Strong reduction
Postprandial hyperglycemia	Strong reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Strong stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Deceleration	No effect
Blood pressure	Reduction	Reduction
Heart rate	No effect or small increase (0–2 bpm)	Moderate increase (2–5 bpm)
Body weight reduction	1–5 kg	2–5 kg
Induction of nausea	20–50%, attenuates slowly (weeks to many months)	20–40%, attenuates quickly (~4–8 weeks)

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to the development of current incretin-based therapies.

Mechanism of Action of Incretin-Based Therapies

Incretin-based therapies can be divided into two subclasses: dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists. Oral DPP-4 inhibitors delay destruction of native GLP-1 by the DPP-4 enzyme system, which increases native GLP-1 levels by two- to threefold (9,10). Injectable GLP-1 receptor agonists raise the level of direct activation of the GLP-1 receptor by about tenfold by action of the molecule on the GLP-1 receptor (9,10). DPP-4 inhibitors cause a glucose-dependent release of insulin from pancreatic β-cells and suppress release of glucagon from α-cells. GLP-1 receptor agonists have this same effect, although quantitatively more so, and some GLP-1 receptor agonists decelerate gastric emptying

(9,10). GLP-1 receptor agonists have also been shown to reach a level of receptor activation that causes central satiety (11). Taken together, these effects of GLP-1 receptor agonists can contribute greatly to glucose control. Differential clinical effects of GLP-1 receptor agonists are summarized in Table 1 (12). Because the glucose-lowering effects of all incretin-based therapies are glucose dependent, they do not typically cause hypoglycemia (unless given with an insulin secretagogue or insulin) or weight gain, and GLP-1 receptor agonists are usually associated with weight loss (12).

Pharmacological Properties of GLP-1 Receptor Agonists

Overall, GLP-1 receptor agonists have widely differing half-lives and dosing frequencies, as well as varying degrees of A1C-lowering ability. The current GLP-1 receptor agonists differ in the extent to which they con-

trol postprandial and fasting plasma glucose (Table 1) (12). Short-acting GLP-1 receptor agonists such as exenatide twice daily (BID) and lixisenatide QD primarily affect postprandial glycemic excursions, with limited impact on fasting plasma glucose. For this reason, they are often referred to as prandial GLP-1 receptor agonists (12,13). In contrast, long-acting GLP-1 receptor agonists, including liraglutide, exenatide once weekly (QW), albiglutide, and dulaglutide, exert their greatest effect on fasting plasma glucose and can, therefore, be classified as nonprandial or fasting GLP-1 receptor agonists (12,14,15).

The safety profiles of exenatide BID and liraglutide QD are quite similar and are primarily characterized by gastrointestinal (GI) adverse events (AEs), predominantly nausea and vomiting (16). Exenatide QW has a markedly reduced incidence of GI AEs compared to other GLP-1 receptor agonists, particularly liraglutide QD (14). All of these incretin drugs are generally safe and effective when used either as monotherapy, as additives to oral antidiabetic agents, or in combination with basal insulin. As a result of these attractive properties, these antidiabetic agents are progressively more studied, better understood, and more often used by PCPs (17).

Lixisenatide: A Safe and Efficacious Option for Type 2 Diabetes Management

Lixisenatide is a prandial GLP-1 receptor agonist that is administered QD and has properties that differentiate it from other agents in its drug class (18). In initial dose-finding studies, lixisenatide was evaluated at several strengths and frequencies to estimate the optimal dosing schedule. It was determined that lixisenatide 20 μg QD produced the best efficacy-to-tolerability ratio (18). This makes lixisenatide unique as the only prandial GLP-1 receptor agonist administered QD. Despite its seemingly short half-life, it offers postprandial glucose reduction

throughout the day with QD dosing (12). Lixisenatide also has the capacity to substantially decelerate gastric emptying, a property that may be lacking in several nonprandial GLP-1 receptor agonists such as exenatide QW and liraglutide (10,12,19).

In the multi-trial GetGoal Program, the efficacy and safety of lixisenatide were investigated in different settings of type 2 diabetes therapy: either as monotherapy; as add-on therapy to metformin, sulfonylureas, or thiazolidinediones (TZDs); or in combination with basal insulin (20–29). When lixisenatide QD was compared to exenatide BID as add-on therapy in type 2 diabetes inadequately controlled by metformin monotherapy, lixisenatide demonstrated noninferiority in terms of A1C reduction compared to exenatide, with a similar percentage of patients reaching their glycemic goal. The incidence of AEs was similar for lixisenatide (70%) and exenatide (72%), although lixisenatide had better overall GI tolerability, including a statistically significant reduction in nausea events compared to exenatide (25 vs. 35%, $P < 0.05$) (24). This finding is clinically significant because nausea is one of the main reasons patients discontinue use a GLP-1 receptor agonist. In the same study, the incidence of hypoglycemia was significantly lower (by sixfold) with lixisenatide compared to exenatide BID (24).

It has been widely hypothesized that a key driver for postprandial normalization of glycemia by GLP-1 receptor agonists is a marked deceleration of gastric emptying, resulting in delayed entry of glucose into the circulation (30). However, there appears to be tachyphylaxis associated with this effect for the long-acting, nonprandial exenatide QW (31). Studies also show that liraglutide, as well as DPP-4 inhibitors such as sitagliptin, do not demonstrate long-term deceleration of gastric emptying (9,32). In contrast, lixisenatide demonstrates significant deceleration of gastric

emptying without tachyphylaxis, which may explain why studies in animals (33,34) and humans (19,35) show better improvement in postprandial glucose excursions and glucagon suppression with lixisenatide versus liraglutide (22,36). Thus, deceleration of gastric emptying appears to be a major factor in lixisenatide's ability to control postprandial glucose excursions.

Glucose excursions depend more on the rate, rather than the amount, of postprandial glucose presentation (36,37). Although research on the clinical effects of GLP-1 receptor agonists has stressed the key contribution of glucose-dependent release of insulin from pancreatic β -cells (17), patients receiving lixisenatide actually seem to produce significantly less total insulin and C-peptide compared to liraglutide-treated patients. This observation may be explained by the significantly greater effect of prandial lixisenatide on deceleration of gastric emptying, which reduces the need for increased insulin production (36).

Studies of lixisenatide in combination with basal insulin have shown promising results that seem to suggest an important role for lixisenatide in treating postprandial plasma glucose (25,26,29,38,39). These studies showed that lixisenatide results in substantial A1C reduction, with a high percentage of patients reaching A1C goals, as well as substantial postprandial plasma glucose control (Table 2) (25). A study that investigated titrated basal insulin dose in patients with type 2 diabetes insufficiently controlled on metformin with or without a TZD showed consistent improvement in A1C reduction with the addition of lixisenatide (26). This may suggest a hidden or residual postprandial plasma control defect, even in patients who are less than optimally titrated on basal insulin. In addition to improvements in A1C, the addition of lixisenatide to basal insulin resulted in weight neutrality and an overall reduction in the insu-

lin dose (with a single daily injection of a fixed dose of GLP-1 receptor agonist) (26,29).

Outlook for the Role of Lixisenatide in Type 2 Diabetes Management

There is growing understanding that type 2 diabetes manifests as a combination of deficits, first in postprandial plasma glucose control, followed by impaired fasting glucose management (40). Indeed, most therapies in the antidiabetic management landscape have hinged on the control of fasting plasma glucose, and most PCPs focus on “fixing the fasting first” as the correct way to manage glucose with insulin. A study by Brown et al. (41) suggests that it takes clinicians nearly a decade to institute any insulin therapy. Another study by Peyrot et al. (42) indicates that most PCPs believe that insulin should be delayed until nothing else works. Clinicians are often reluctant to add mealtime insulin to address postprandial glucose excursions because of fear of multiple daily injections and an increased risk of hypoglycemia. Perhaps such attitudes may contribute to overuse of basal insulin with associated weight gain and increased risk of hypoglycemia (43).

As the impact of postprandial glucose excursions becomes more fully understood, it seems reasonable that future antidiabetic therapy will simultaneously address postprandial and fasting plasma glucose control. The properties of lixisenatide, as demonstrated in the studies reviewed above, make it a suitable addition to basal insulin, after fasting plasma glucose has been addressed, to better control postprandial glucose. Lixisenatide is associated with a lower incidence of hypoglycemia and weight gain, which makes it an interesting alternative to rapid-acting mealtime insulin for postprandial glycemic control.

Given the increasing number of patients with type 2 diabetes and the shrinking cadre of physicians (both PCPs and endocrinologists), clinicians will be more pressed to adopt safe,

TABLE 2. Improvements in A1C Reduction and Postprandial Glucose Control for Lixisenatide as Add-On Therapy to Basal Insulin (25)

Parameter	Lixisenatide (n = 146)	Placebo (n = 154)	P
A1C reduction (%)			
Mean A1C at baseline	8.5	8.5	
LS mean change at week 24	-0.77	0.11	
LS mean difference vs. placebo (95% CI)	-0.88 (-1.12 to -0.65)		<0.0001
A1C goals at week 24 (%)			
A1C ≤6.5%	17.8	1.3	<0.0001
A1C <7.0%	35.6	5.2	<0.0001
2-hour PPG (mg/dL)			
n	131	142	
LS mean change at week 24	-143.3	-2.5	
LS mean difference vs. placebo (95% CI)	-140.9 (-160.0 to -121.9)		<0.0001
Glucose excursion (mg/dL)			
n	131	142	
LS mean change at week 24	-127.6	2.5	
LS mean difference vs. placebo (95% CI)	-130.0 (-148.5 to -111.6)		<0.0001

CI, confidence interval; LS, least squares; PPG, postprandial glucose.

effective, easy-to-deliver treatment strategies that can fully control their patients' blood glucose throughout the day. Currently available incretin-based drugs have helped to meet the treatment needs of type 2 diabetes, but none fulfill all of the criteria of an optimal prandial GLP-1 receptor agonist. Lixisenatide offers important benefits, including its delivery as a once-daily, fixed-dose injection and its substantial deceleration of gastric emptying. These benefits lead to pronounced decreases in postprandial glucose and a beneficial effect on body weight, in conjunction with an acceptable safety and tolerability profile and a minimal risk of hypoglycemia compared to exenatide.

Addendum

Since the writing of this article, lixisenatide has been approved and is in use in Europe, and both lixisenatide and a combination of insulin glargine (Lantus) and lixisenatide (LixiLan) have been submitted to the U.S. Food and Drug Administration for approval.

Duality of Interest

Dr. Shaefer is a speaker for AstraZeneca Global, Boehringer Ingelheim/Eli Lilly, Bristol-Myers Squibb/AstraZeneca, Forrest Pharmaceuticals, Janssen Pharmaceuticals, Novartis, Sanofi US, Sanofi Global, and Vivus. He is an advisory board member for Bristol-Myers Squibb/AstraZeneca, Eli Lilly US, Eli Lilly Global, Janssen Pharmaceuticals, Sanofi US, and Sanofi Global. No other potential conflicts of interest relevant to this article were reported.

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