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REVIEW

Mechanisms and Clinical Efficacy of Lixisenatide for the Management of Type 2 Diabetes

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ABSTRACT

Introduction: "Incretin-based" therapies, such as the glucagon-like peptide-1 (GLP-1) receptor agonists, represent a major advance in type 2 diabetes mellitus (T2DM) treatment. GLP-1 receptor agonists differ substantially in their duration of action, frequency of administration and clinical profile.

Methods: This article reviews the mechanisms of action and clinical evidence for GLP-1 receptor targeting and discusses differences between GLP-1 therapies, focusing particularly on clinical data for the GLP-1 receptor agonist, lixisenatide.

Results: GLP-1 therapies target islet cell "defects" of insufficient insulin and excessive glucagon secretion in T2DM, in a glucose-dependent manner, with minimal risk of hypoglycemia. Different GLP-1 therapies exert differential effects on fasting and postprandial glycemia (both being major determinants of glycemic control). They also slow gastric emptying to different extents, probably accounting for different effects to reduce postprandial glycemia. The GetGoal phase 3 studies in T2DM have confirmed the efficacy of once-daily lixisenatide in reducing plasma glucose and glycated hemoglobin (HbA_{1c}), with a pronounced lowering of postprandial plasma glucose (PPG), as monotherapy and as add-on to oral antidiabetic drugs and to basal insulin. Lixisenatide's ability to diminish PPG is probably partly mediated by its marked ability to delay gastric emptying. Lixisenatide is generally well tolerated, with possibly better gastrointestinal tolerability and lower risk of hypoglycemia than exenatide immediate release. Lixisenatide is associated with a beneficial effect on weight, with either no change or a decrease in body weight when administered as add-on therapy to basal insulin in overweight patients with T2DM.

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Conclusions: Lixisenatide improves glycemic control, by primarily affecting PPG, while preventing weight gain or reducing body weight with a low risk of hypoglycemia in T2DM. Lixisenatide is likely to represent a significant advance in the management of T2DM, perhaps particularly in those patients with relatively faster gastric emptying and lower levels of HbA_{1c}, including those receiving basal insulin.

Keywords: Exenatide; Gastric emptying; Glucagon-like peptide-1 receptor agonists; Hypoglycemia; Incretin therapies; Liraglutide; Lixisenatide; Pharmacokinetics; Postprandial plasma glucose; Type 2 diabetes mellitus

INTRODUCTION

A number of therapeutic options are available for the management of type 2 diabetes mellitus (T2DM), as indicated by the recent American Diabetes Association/European Association for the Study of Diabetes guidelines [1]. These therapies are associated with different adverse effects; notably, the use of insulin and insulin secretagogs is associated with an increased propensity for hypoglycemia and weight gain [2]. The recent availability of "incretin-based" therapies, comprising of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, represents a major advance given that these drugs do not increase the risk of hypoglycemia significantly. DPP-4 inhibitors are weight neutral, while the use of GLP-1 receptor agonists is associated with modest weight loss [1, 2]. The development of these drugs has followed the recognition that the incretin system is pivotal to the regulation of blood glucose homeostasis. It was reported in 1964 that the insulin response to an enteral, or oral, glucose load is substantially greater than that induced by an iso-glycemic intravenous glucose load [3, 4]. In healthy individuals, this so-called "incretin effect" accounts for 50–70% of postprandial insulin secretion [5]. The two known incretin hormones are GLP-1 (secreted predominantly from the distal small intestine and colon) and gastrointestinal insulinotropic polypeptide (GIP; secreted mainly from the proximal small intestine). The insulinotropic property of GIP was documented in 1973 [6] and that of GLP-1 in 1985 [7]. The release of incretin hormones is stimulated by the interaction of nutrients (and also bile salts in the case of GLP-1) with the intestine. Both are rapidly degraded in the circulation by a ubiquitous enzyme called DPP-4, so that the plasma half-life of the active molecules is only a few minutes [8, 9]. In 1986, Nauck and colleagues [10] reported that the magnitude of the incretin effect was diminished in patients with T2DM. While this may potentially represent an epiphenomenon of pancreatic beta-cell failure, it is clear that the secretion of both GIP and GLP-1 is relatively intact in T2DM; but while the insulinotropic property of GLP-1 is preserved, that of GIP is markedly diminished, probably partly as an effect of hyperglycemia [11]. Pharmaceutical development has thus hitherto focused primarily on agents based on the action of GLP-1, i.e., DPP-4 inhibitors and GLP-1 receptor agonists, which are resistant to degradation by DPP-4 [12]. A fundamental advantage of GLP-1-based therapy is that it targets the islet cell "defects" of insufficient insulin, and excessive glucagon, secretion in T2DM. Importantly, the insulinotropic and glucagonostatic properties of GLP-1 are glucose-dependent, with a threshold for these effects of approximately 8 mmol/L, so that there is minimal, if any, risk of hypoglycemia. These drugs also target fasting, as well as pre and postprandial glycemia; the latter is now recognized as a major determinant of "average" glycemic control, as assessed by

glycated hemoglobin (HbA_{1c}), particularly as glycemic control improves [1]. Several GLP-1 receptor agonists are available and are increasingly used both as monotherapy and as "add-on" to other agents, particularly metformin, and more recently, basal insulin [13–15]. Unlike DPP-4 inhibitors (which are administered orally), there are substantial differences between GLP-1 receptor agonists (which are administered subcutaneously) in terms of their duration of action and consequent frequency of administration.

This review addresses the mechanisms of action and clinical efficacy of GLP-1 receptor agonists, with a particular focus on a novel agent in this class, lixisenatide.

METHODS

Pubmed was searched for English language articles that evaluated the pharmacokinetics, efficacy, safety and mode of action of lixisenatide (without time limits). The search parameters were "glucagon-like peptide-1 receptor agonists," "lixisenatide," "efficacy," "safety," "mechanism of action," and "pharmacokinetics." Original research articles, reviews and other articles of interest were reviewed. References of key reviews were also reviewed to ensure that all data sources were captured. In addition, a number of abstracts and posters on lixisenatide presented at key diabetes congresses were also reviewed when available in the public domain. From these sources, the most important information was identified for inclusion in this review. Abstracts and posters citing data that are now published were excluded from this review.

The GLP-1 Receptor as a Therapeutic Target

GLP-1 receptor agonists target several metabolic abnormalities in the T2DM phenotype, and GLP-1 receptors are expressed widely throughout multiple body systems, including the pancreas, brain, heart, kidney, and gastrointestinal tract.

It has generally been assumed that GLP-1 regulates glucose homeostasis through effects on islet cell function [16–18], which are certainly important, especially in relation to the glucose dependency of the insulinotropic and glucagonostatic properties of GLP-1 [19], and are of particular relevance to fasting glycemia. However, because the human stomach empties at an overall rate of 1–4 kcal/min in health [20, 21], most humans are predominantly in the postprandial or postabsorptive state, with the duration of fasting limited, in most cases, to perhaps about 4 h before breakfast. Moreover, gastric empting is often abnormally delayed (and occasionally, more rapid) in patients with T2DM and is a major determinant of postprandial glycemia [22–24]. In T2DM patients with delayed emptying, the magnitude of this delay is often modest [22–24], hence the fact that both endogenous and exogenous GLP-1 slow gastric emptying is of fundamental significance. Moreover, the secretion of GLP-1 is dependent on the small intestinal glucose load being released in much greater amounts when the rate of carbohydrate exposure is at the upper end of the normal physiological range [25]. Using the GLP-1 receptor antagonist, exendin (9–39), it was shown that endogenous GLP-1 is a physiologic modulator of gastric emptying [26]. When GLP-1 was administered exogenously to healthy individuals [27, 28] and patients with T2DM [29], there was an overall marked (but variable) slowing of gastric emptying. The reduction in postprandial glycemia induced by acute administration of GLP-1 was shown to be related to the magnitude of the slowing of gastric emptying [28];

the latter is greater when "baseline" gastric emptying is relatively more rapid [30]. That the reduction in postprandial glycemia induced by exogenous GLP-1 is associated with a reduction, rather than an increase, in insulin indicates that slowing of gastric emptying outweighs the insulinotropic property of GLP-1 in this situation [28, 29, 31]. Not surprisingly, administration of the gastrokinetic drug, erythromycin, suppressed the GLP-1-induced slowing of gastric emptying and attenuated its effect to reduce postprandial glycemia [32]. Therefore, it is arguable whether or not GLP-1 should be regarded as a true incretin, at least postprandially. A recent study suggests that the slowing of gastric emptying by exogenous GLP-1 may be subject to tachyphylaxis with sustained exposure [33]. When two drinks were given to healthy individuals at an interval of 4 h, GLP-1 slowed gastric emptying of both drinks, but the magnitude of the slowing of the second drink was less. It was suggested that tachyphylaxis may occur at the level of the vagus nerve [33]. While the study had methodological limitations, the conclusions are likely to be valid and of major relevance to the effects of different GLP-1 receptor agonists.

GLP-1 is also involved in the regulation of appetite and energy intake. For example, in obese individuals there was a reduction in hunger and food consumption after infusion of GLP-1 [34], and in patients with T2DM, a continuous, subcutaneous infusion of GLP-1 over a 6-week period reduced appetite and resulted in an average weight loss of 1.9 kg [35]. Studies in animals suggest that GLP-1 has the capacity to promote β-cell proliferation [36], inhibit apoptosis [37], and thereby preserve or expand β-cell mass [38]. It remains to be determined whether this is also the case in human T2DM. Therefore, GLP-1 has diverse effects of relevance to blood glucose homeostasis.

Differences Between GLP-1 Receptor Agonists

Three GLP-1 receptor agonists are currently approved for the management of T2DM, and several agents are in late-stage development. Exenatide immediate release (IR) was approved in Europe in 2006 and is a "short-acting" GLP-1 receptor agonist (mean half-life of 2.4 h) given as a twice-daily injection 30–60 min before the first and last meal of the day [39]. In some European countries, exenatide is also available as an extended-release formulation, which is given as a once-weekly injection [40]. Liraglutide was approved in Europe in 2009 and is a "long-acting" GLP-1 receptor agonist given as a once-daily injection independent of meals. Liraglutide has a half-life of 11–15 h and is designed to provide sustained GLP-1 activation throughout the day [41] (Table 1) [39, 41–46]. Exenatide, a synthetic version of exendin-4, originally isolated from the saliva of the Gila monster lizard, is a GLP-1 receptor agonist exhibiting approximately 53% homology to native GLP-1. In contrast, liraglutide is a GLP-1 analog and was developed specifically for use in T2DM.

All GLP-1 receptor agonists appear to have the same fundamental mode of action on the GLP-1 receptor. Meta-analyses and randomized, controlled trials indicate that these agents improve HbA_{1c} on average by about 1%, with a low risk of hypoglycemia, reduce body weight by 1–4 kg per annum, and are generally well tolerated. Although gastrointestinal adverse events (AEs) such as nausea and diarrhea are common, in most cases they dissipate with ongoing use [47–49]. For example, gastrointestinal AEs resolve within 6–8 weeks in most patients and both their incidence and severity can be reduced using a dose-escalation strategy [50, 51]. GLP-1 receptors are widely expressed in cardiovascular tissue, and

Table 1 Pharmacologic characteristics of currently available GLP-1 receptor agonists and lixisenatide

Drug	Administration	$t_{1/2}$	t_{max}	Exposure	Sustained effect to slow gastric emptying
Exenatide IR [39]	Twice daily	2.4 h	2.1 h	Intermittent	Yes
Exenatide ER [45]	Once weekly	2.4 h	2 weeks[a]	Continuous	Minimal[b]
Liraglutide [41]	Once daily	11–15 h	9–12 h	Continuous	Minimal[c]
Lixisenatide[d] [46]	Once daily	2.8 h	1.25 h	Intermittent	Yes

ER extended release, *GLP-1* glucagon-like peptide-1, *IR* immediate release, $t_{1/2}$ terminal half-life, t_{max} time to maximum plasma concentration

[a] First peak, a second peak occurs at 6–7 weeks

[b] 75% less efficacy versus exenatide IR in head-to-head study [44]

[c] Flint et al. [42] and Degn et al. [43] analysis ongoing

[d] 20 μg dose

cardiovascular effects, particularly a modest increase in heart rate, have been reported with the use of GLP-1 receptor agonists [50, 52, 53].

GLP-1 receptor agonists exhibit differences in their effects on pre and postprandial glucose [54]. For example, in a direct comparison between liraglutide and exenatide IR in patients with T2DM inadequately controlled on metformin or sulfonylurea, liraglutide 1.8 mg once daily (n = 233) reduced mean fasting plasma glucose (FPG) versus exenatide (estimated treatment difference –1.01 mmol/L; $P < 0.0001$), while exenatide had a greater effect on PPG excursions (breakfast: estimated treatment difference 1.33 mmol/L; $P < 0.0001$; dinner: estimated treatment difference 1.01 mmol/L; $P = 0.0005$) [51]. These differences are likely to reflect the pharmacokinetic profile of GLP-1 receptor activation, as a result of the impact on the slowing of gastric emptying, and hence, postprandial glycemic excursions. As is the case with native GLP-1 [30], the magnitude of the effect of GLP-1 receptor agonists to slow gastric emptying in T2DM appears to be dependent on the baseline rate of emptying, so that the effect is greater in those with more rapid emptying initially [55]. Furthermore, the reduction in postprandial glycemia and the impact on postprandial insulin induced by GLP-1 receptor agonists are related to the slowing of gastric emptying [55]. Scintigraphy is the "gold standard" technique to quantify gastric emptying [56, 57], while the use of stable isotope breath tests and ultrasonography are acceptable alternatives [57–59]. However, in many studies relating to the effect of GLP-1 receptor agonists on gastric emptying, the latter has been assessed using the less-than-optimal paracetamol absorption method [42–44, 60]. With the latter technique, it has been reported in rats that the delay of gastric emptying induced by liraglutide diminishes within 14 days, whereas the comparable initial delay induced by exenatide IR is sustained (Fig. 1) [60]. In patients with T2DM, after 14 weeks' administration, exenatide IR slowed paracetamol absorption significantly, while exenatide long-acting release (LAR) had no significant effect [44]. Liraglutide does, however, have a modest effect to delay paracetamol absorption after administration for 3 weeks in patients with T2DM, which correlates with the reduction in postprandial glucose [42]. In contrast, exenatide IR has been

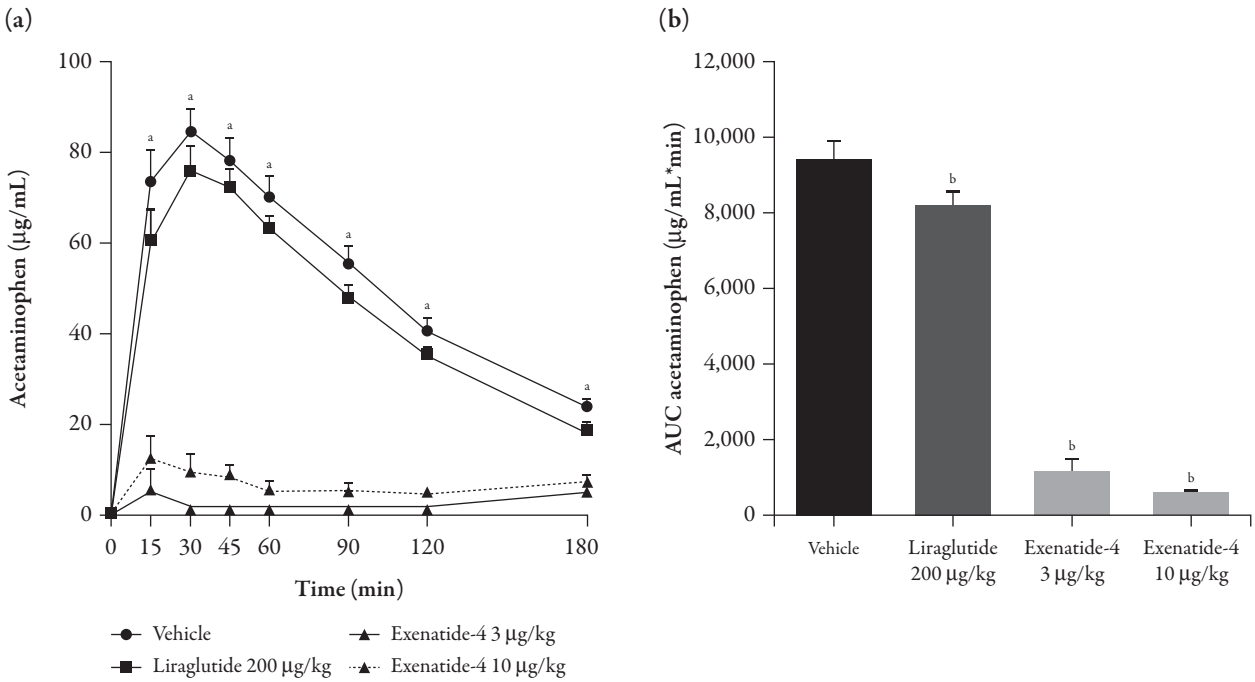

Fig. 1 Study in rats demonstrating tachyphylaxis in the slowing of gastric emptying induced by liraglutide, but not exenatide IR. Gastric emptying was assessed using a standard acetaminophen release assay. After the acute test, rats were dosed twice daily for 14 days. (**a**) Plasma levels of acetaminophen following subcutaneous administration (at t = −30 min) of vehicle, liraglutide or exenatide on day 14; (**b**) $AUC_{(0–180\ min)}$. The data show only a slight (~ 5%) inhibition of gastric emptying in liraglutide-treated rats, while in exenatide-treated rats, gastric emptying was dramatically reduced. Reproduced with permission from Jelsing J, et al. Diabetes Obes Metab. 2012;14:531–8. [60]. [a]Exenatide 3 and 10 µg/kg significantly different from vehicle, [b]exenatide 3 and 10 µg/kg and liraglutide 200 µg/kg significantly different from vehicle ($P < 0.05$ for both) $AUC_{0–180\ min}$ area under the curve at 0–180 min, *IR* immediate release

shown to slow gastric emptying markedly in T2DM after administration for 5 days, as assessed by scintigraphy [55]. These observations are presumably attributable to the "tachyphylaxis" phenomenon reported by Nauck et al. [33]. The implications are that "baseline" gastric emptying and the priority for reducing postprandial glucose excursions are likely to be relevant to the choice of GLP-1 receptor agonist in patients with T2DM. This includes the potential combination of basal insulin and a GLP-1 receptor agonist, for which there is a persuasive rationale, i.e., insulin therapy primarily targets preprandial glucose and causes hypoglycemia and weight gain, while some GLP-1 receptor agonists predominantly target postprandial glucose by slowing gastric emptying, and their use is associated with a low risk of hypoglycemia and modest weight loss. Therefore, the combined use of basal insulin with a GLP-1 receptor agonist has the potential to optimize glycemic control, with a limited risk of hypoglycemia and without weight gain. There is now evidence that this approach is effective. For example, in a recent study by Buse et al. [53] in patients with T2DM, exenatide IR added on to basal insulin glargine improved glycemic control substantially, with a reduction in HbA_{1c} of 1.74% after 30 weeks' treatment compared with 1.04% with placebo, without an increased risk of hypoglycemia or weight gain.

Lixisenatide: A Novel GLP-1 Receptor Agonist

Lixisenatide is a new once-daily prandial GLP-1 receptor agonist that was approved by the European Medicines Agency in February 2013 for the management of T2DM. Lixisenatide is a synthetic version of exendin-4 that is resistant to degradation by DPP-4 as a result of C-terminal modification with six lysine residues and one proline deletion [61]. Lixisenatide is unique in that it is "short-acting," but administered as a once-daily dose; this is believed to be partly due to its marked ability to delay gastric emptying (Table 1) [61]. Lixisenatide has now been well characterized in pharmacokinetic and pharmacodynamic studies and its efficacy and safety in patients with T2DM has been evaluated in an extensive clinical development program known as the GLP-1 agonist AVE0010 in paTients with type 2 diabetes mellitus for Glycemic cOntrol and sAfety evaLuation (GetGoal) phase 3 clinical trial program. Notably, this program includes a study as add-on to basal insulin in Asian patients with T2DM, who often have a pathophysiology of insulin deficiency, rather than insulin resistance and in whom GLP-1 secretion may be impaired [62–64].

RESULTS

Pharmacokinetic and Dosing Studies

Lixisenatide exhibits dose-dependent pharmacokinetics. In a 4-week, randomized, placebo-controlled, dose-ranging study in 64 patients with T2DM, using an ascending dose range of 5–20 µg once daily (increased every fifth day in increments of 2.5 µg), steady-state plasma concentrations increased in proportion to the dose administered (5 µg, 10 µg, and 20 µg). The mean area under the curve (AUC) and peak plasma concentration also increased according to the dose and dose frequency. Peak plasma concentrations were achieved within 1.25–2.25 h (depending on dose) [45]. All lixisenatide doses (5–20 µg) were associated with decreased AUC for PPG versus placebo, with the greatest decrease seen for the lixisenatide 20 µg dose. The median drug half-life was 2.8 h for lixisenatide 20 µg (range 2.7 h in lixisenatide 10 µg once daily to 4.3 h in lixisenatide 5 µg twice daily) [46] (Table 1).

In a 13-week, dose–response study in 542 patients with T2DM inadequately controlled on metformin, lixisenatide 5–30 µg once or twice daily reduced HbA_{1c} levels in a dose-dependent manner; respective mean reductions for 5, 10, 20, and 30 µg doses were 0.47%, 0.50%, 0.69%, and 0.76% on once-daily and 0.65%, 0.78%, 0.75%, and 0.87% on twice-daily administration versus 0.18% with placebo (all $P < 0.01$ vs. placebo). The 20 µg once-daily dosage demonstrated the best efficacy to tolerability ratio [65].

Mechanisms of Efficacy

The mechanisms by which lixisenatide exerts its glucose-lowering effect have been investigated in several studies, which have demonstrated effects of lixisenatide on multiple factors involved in glucose regulation [66–68].

Two parallel, single-dose studies demonstrated that lixisenatide 20 µg daily restores first and second-phase insulin responses and accelerates glucose disposition. In both studies, subjects received lixisenatide 20 µg or matching placebo 2 h before 0.3 g/kg intravenous glucose challenge, and insulin secretion was assessed by C-peptide deconvolution [66, 67]. In the first study, conducted in 20 healthy subjects, lixisenatide enhanced first-phase insulin secretion ($AUC_{0–10\ min}$) 2.4-fold and second-phase by ($AUC_{10–120\ min}$) 0.9-fold versus placebo. Glucose disposition was also accelerated 2.3-fold,

and a reduction in blood glucose below counterregulatory thresholds (<3.9 mmol/L) was evident in some subjects [66]. The second study was conducted in 22 patients with "early-stage" T2DM and 20 healthy subjects. In the healthy subjects, lixisenatide enhanced first and second-phase insulin secretion by 2.4 and 0.8-fold versus placebo, respectively, while in patients with T2DM, lixisenatide enhanced first and second-phase insulin secretion by 2.8 and 1.6-fold versus placebo, respectively. Glucose disposition was increased by 2.3 and 1.8 in healthy subjects and patients with T2DM, respectively [67].

The comparative efficacy of lixisenatide versus liraglutide in reducing PPG concentrations was evaluated in a 4-week, randomized, open-label study of lixisenatide 20 µg once daily (n = 77) versus liraglutide 1.8 mg once daily (n = 71) in patients with T2DM suboptimally controlled on metformin [52]. The primary endpoint was the change in PPG from baseline to week 4 based on a standardized breakfast test. Lixisenatide administration resulted in greater reductions in both PPG (glucose $AUC_{00:30–04:30\ h}$) ($P < 0.0001$) and in maximum PPG excursions versus liraglutide (estimated treatment difference

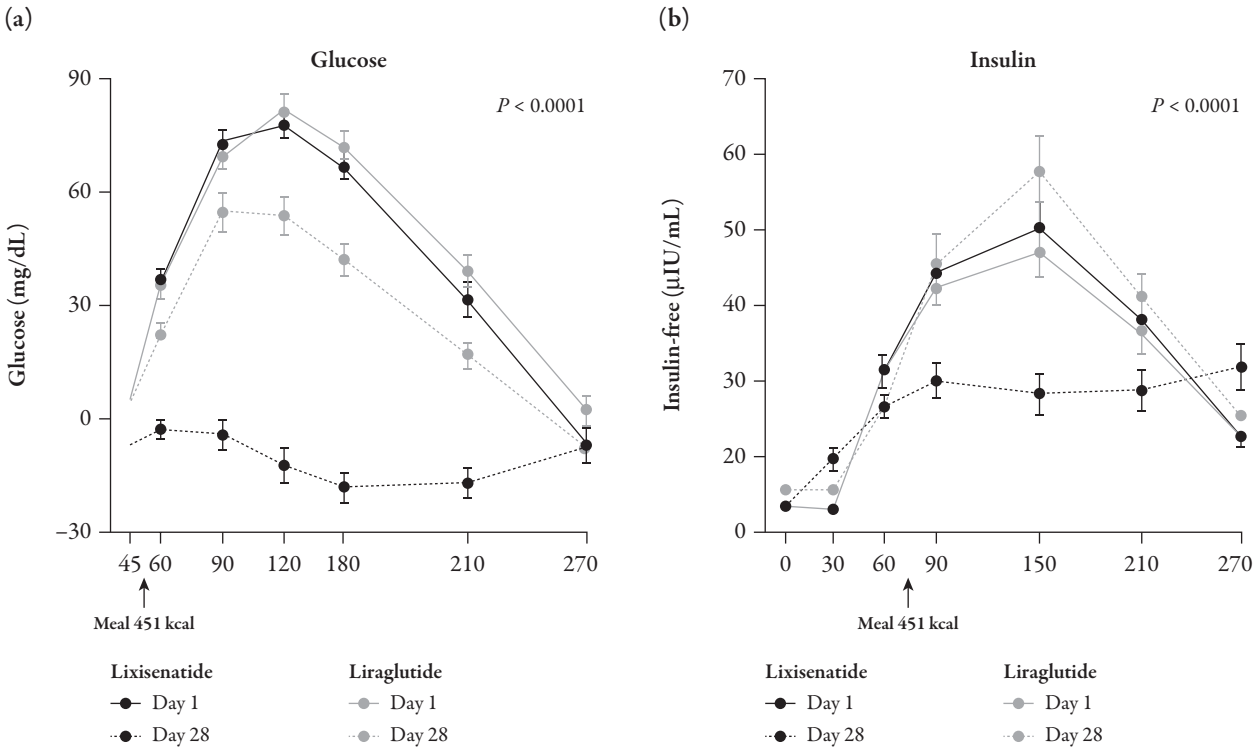

Fig. 2 Changes in postprandial glucose ($AUC_{00:30–04:30\ h}$) and insulin ($AUC_{00:30–04:30\ h}$) after 4 weeks' administration of lixisenatide 20 µg once daily, or liraglutide 1.8 mg once daily in patients with T2DM insufficiently controlled on metformin. At baseline (day −1) and day 28, all participants received a standardized breakfast test (60.6% carbohydrates, 12.4% protein, 26.9% fat, 451 kcal in total). Patients received lixisenatide 20 µg (n = 77) or liraglutide 1.8 mg (n = 71), both administered once daily subcutaneously 30 min before breakfast. Measurements were performed on day −1/day 1 and on day 28/29 over a 24-h period following breakfast. After 4 weeks of treatment, lixisenatide administration resulted in a much greater reduction in (**a**) postprandial plasma glucose and (**b**) insulin, compared with liraglutide, both $P < 0.0001$. Reproduced/modified with permission from Kapitza C, et al. Poster presented at the 21st World Diabetes Congress, Dubai, UAE, December 8 2011 (Absract D–0740) [52]. $AUC_{00:30–04:300h}$ area under the curve from 00:30 to 04:30 h; *T2DM* type 2 diabetes mellitus

–2.53 mmol/L [–45.5 mg/dL]; $P < 0.0001$) (Fig. 2a) [52], so that at study end, a greater proportion of lixisenatide-treated patients achieved 2-h PPG levels <7.77 mmol/L (<140 mg/dL) compared with liraglutide-treated patients (69% vs. 29%, respectively). Postprandial insulin (Fig. 2b) and C-peptide levels were markedly reduced with lixisenatide compared with liraglutide ($P < 0.0001$ for both). Lixisenatide also decreased post meal glucagon when compared with liraglutide (treatment difference –21.2 h.pg/mL; $P = 0.032$). Mean HbA_{1c} and body weight decreased in both groups. Both treatments were reasonably well tolerated; nausea, diarrhea, and vomiting were reported in 22.1%, 2.6%, and 10.4% of patients for lixisenatide and 22.5%, 15.5%, and 7.0% for liraglutide, respectively.

Further investigation demonstrated that the reduction in PPG observed with lixisenatide is accompanied by a substantial slowing of gastric emptying, which would account for the observed reduction in postprandial insulin. In a randomized, double-blind, 4-week trial in patients with T2DM, using an ascending dose range of 5–20 μg once daily or twice daily (increased every fifth day in increments of 2.5 μg), lixisenatide 20 μg reduced PPG after breakfast ($P < 0.0001$), lunch ($P < 0.0001$), and dinner ($P < 0.05$) when compared with placebo, with proportionally greater reductions after breakfast than after lunch and dinner when administered in the morning. These reductions were accompanied by a slowing in gastric emptying of breakfast as assessed by ^{13}C-octanoic acid breath test (mean change from baseline [± standard deviation (SD)] in mean gastric emptying half-emptying time –24.1 ± 133.1 min vs. 211.5 ± 278.5 min for lixisenatide and placebo, respectively; $P < 0.01$). It should be appreciated that the rate of gastric emptying was markedly reduced despite glucose lowering, an effect that would favor more rapid emptying [69]. Moreover, there was an inverse relationship between PPG and the rate of gastric emptying with lixisenatide 20 μg ($r^2 = 0.51$; $P < 0.05$) [68], as has been reported to be the case with exogenous GLP-1 [28] and exenatide IR [55]. Accordingly, lixisenatide, like other GLP-1 receptor agonists, has the capacity to stimulate insulin and suppress glucagon secretion and also markedly reduce postprandial glycemic excursions, probably predominantly by slowing gastric emptying.

GetGoal: The Lixisenatide Phase 3 Clinical Trial Program

The safety and efficacy of lixisenatide 20 μg once daily has been evaluated in adult patients with T2DM in the GetGoal phase 3 clinical trial program, which was initiated in 2008 and has hitherto enrolled more than 5,000 patients globally. An overview of available patient characteristic data from the studies included in the program is shown in Table 2 [62, 70–76]. In this series of randomized, placebo-controlled trials, lixisenatide was evaluated across the spectrum of T2DM care as monotherapy, as add-on therapy to metformin, sulfonylureas, or thiazolidinediones, and in combination with basal insulin. Three studies investigated the combined effects of lixisenatide and basal insulin with the rationale that targeting both PPG (with lixisenatide) and FPG and preprandial plasma glucose (with basal insulin) may provide additive effects, leading to enhanced glycemic control [62, 70, 71]. In all of the completed studies, the efficacy of lixisenatide once daily in reducing blood glucose levels, with a pronounced effect on PPG, has been demonstrated.

Effect of Lixisenatide as Monotherapy and as "Add-On" to Oral Antidiabetic Agents

The effect of lixisenatide on glycemia both as monotherapy and as "add-on" to oral antidiabetic agents (OADs) has been evaluated

Table 2 Summary of patient characteristics in the GetGoal studies

Study	*N*	Age (mean, years)		Diabetes duration (years)		Male (%)		Baseline BMI (mean, kg/m^2)		Race, % (Caucasian/black/Asian)		Baseline HbA_{1c} (%)	
		LIXI	PBO/Com	LIXI	PBO/Com	LIXI	PBO/Com	LIXI	PBO/Com	LIXI	PBO/Com	LIXI[a]	PBO/Com
GetGoal-F1 [76]	482	55.4	58.2	5.0[b]	4.9[b]	44	45	33.0	32.4	88/1/8[c]	93/1/6[c]	7.99	8.03
GetGoal-M [72]	680	54.7		6.1[d]		NA		32.9		NA		8.06	
GetGoal-S [73]	859	57.0	57.8	8.0[b]	8.5[b]	49	53	30.1	30.4	52/3/45	53/3/44	8.28	8.22
GetGoal-P [74]	479	55.8		8.1[d]		NA		33.9		NA		8.08	8.05
GetGoal-X[e] [75]	634	57.3	57.6	5.6[b]	5.8[b]	47	59	33.7	33.5	93/3/1	92/3/1	7.95	7.97
GetGoal-L [70]	493	NA		12.5[d]		NA		32.1		NA		8.39	8.38
GetGoal-L-Asia [62]	311	58.7	58.0	13.7[d]	14.1[d]	69	80	25.4	25.2	0/0/100	0/0/100	8.54	8.52
GetGoal-Duo-1 [71]	446	56.2		9.2[d]		NA		31.8		NA		8.60	8.60

BMI body mass index, *Com* comparator, *HbA_{1c}* glycated hemoglobin, *LIXI* lixisenatide, *NA* data not yet published, *PBO* placebo

[a] One-step titration

[b] Median

[c] Population included other races

[d] Mean

[e] Comparator was exenatide immediate release

in a series of trials, with HbA_{1c} as the primary endpoint. These studies have established the efficacy of lixisenatide both as monotherapy and as add-on to OADs, with an effect of decreasing HbA_{1c} comparable with that of exenatide IR, and a particularly pronounced effect in reducing PPG excursions.

Fasting Plasma Glucose

As monotherapy, lixisenatide administration resulted in reductions in FPG versus placebo (least squares [LS] mean difference vs. placebo –1.1 mmol/L [–19.8 mg/dL]; $P < 0.0001$ for lixisenatide one-step titration) [77]. As add-on to metformin, lixisenatide, in a morning dose, led to FPG reductions of –1.19 (–21.4 mg/dL; $P < 0.005$ vs. placebo) [72]; as add-on to sulfonylurea, to a reduction of –0.99 (–17.8 mg/dL; $P < 0.0001$ vs. placebo) [73]; and as add-on to thiazolidinediones, to FPG reductions of –0.84 (–15.1 mg/dL; $P < 0.0001$ vs. placebo) [74]. In GetGoal-X versus exenatide IR, improvements in mean FPG were comparable between lixisenatide once daily and exenatide twice daily (LS mean change from baseline –1.2 mmol/L [–22 mg/dL] and –1.4 mmol/L [–26 mg/dL], respectively) [75].

Postprandial Glucose

As monotherapy in GetGoal-MONO, lixisenatide had a pronounced effect on PPG associated with breakfast, with improvements in 2-h postprandial glucose levels ($P < 0.001$ vs. placebo) and a 75% reduction versus placebo in the postprandial glucose excursion, as measured during a standardized breakfast (Fig. 3) [77]. Similar results have been demonstrated for

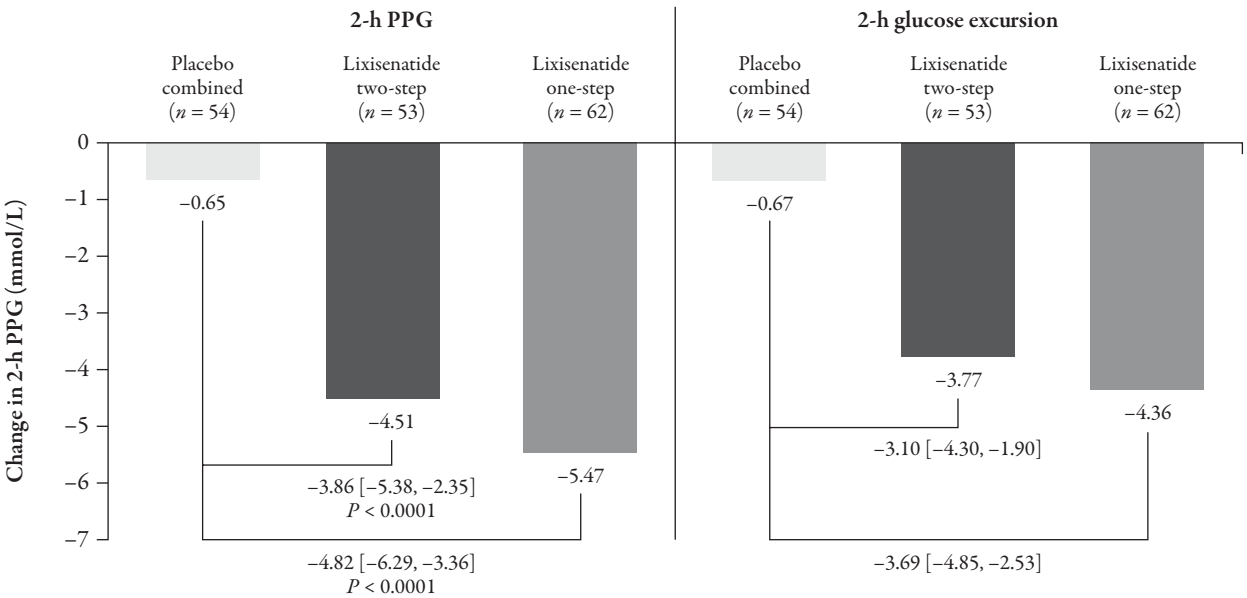

Fig. 3 Changes in 2-h postprandial glucose and 2-h glucose excursion after 12 weeks of treatment with lixisenatide 20 μg two-step (10 μg for 1 week, 15 μg for 1 week, and then 20 μg; $n = 120$), lixisenatide one-step (10 μg for 2 weeks and then 20 μg; $n = 119$), placebo two-step ($n = 61$), or placebo one-step ($n = 61$) (placebo groups were combined for analyses). Data are from patients with T2DM not receiving glucose-lowering therapy undergoing a standardized breakfast meal. Glucose excursion = 2-h PPG, plasma glucose 30 min before the meal test before study drug administration. Lixisenatide one-step and two-step titration reduced both 2-h PPG and 2-h glucose excursions versus placebo. Data shown are mean ± SD. Reproduced with permission from Fonseca VA, et al. Diabetes Care. 2012;35:1225–31 [77]. *PPG* postprandial glucose, *T2DM* type 2 diabetes mellitus

lixisenatide in patients suboptimally controlled on metformin in the GetGoal-M study [72] and sulfonylureas in the GetGoal-S study [73].

Glycated Hemoglobin

As monotherapy in a 12-week trial (GetGoal-MONO), lixisenatide administration resulted in reductions in HbA_{1c} versus placebo (–0.85 for one-step and –0.73 for two-step titration vs. –0.19 for placebo; $P < 0.0001$) and increased the number of patients achieving HbA_{1c} <7% (46.5% one-step, 52.2% two-step, 26.8% placebo) and HbA_{1c} of ≤6.5% (25.4% one-step, 31.9% two-step, 12.5% placebo; $P < 0.01$) [77].

Several trials have demonstrated the capacity of lixisenatide to lower HbA_{1c} as add-on to other therapies. For example, as add-on to metformin in patients insufficiently controlled on metformin alone in two 24-week trials (GetGoal-M and GetGoal-F1; one-step and two-step dose increase regimens of lixisenatide), lixisenatide reduced HbA_{1c} from baseline (HbA_{1c} change from baseline [mean baseline HbA_{1c} 8.06%] in GetGoal-M –0.87 and –0.38 for lixisenatide morning dose and placebo, respectively; $P < 0.0001$) [72] and increased the proportion of patients achieving HbA_{1c} goals (GetGoal-F1 47.4% achieved HbA_{1c} <7% for lixisenatide one-step titration vs. 24.1% for placebo [$P < 0.001$] and 25.6% achieved HbA_{1c} <6.5% for lixisenatide one-step titration vs. 7.6% for placebo; $P < 0.0001$) [76]. The safety and efficacy of lixisenatide once daily in patients inadequately controlled on metformin has been compared directly with exenatide IR twice daily as add-on therapy in the GetGoal-X study [75]. The primary objective of this randomized, open-label, 24-week trial was to demonstrate noninferiority of lixisenatide 20 µg once daily ($n = 318$) to exenatide 10 µg twice daily ($n = 316$) for HbA_{1c} reduction. Lixisenatide did demonstrate noninferiority to exenatide IR at the end of the study, the proportion of subjects achieving HbA_{1c} <7.0% was comparable between treatment groups (48.5 vs. 49.8 for lixisenatide and exenatide, respectively) [75]. Lixisenatide has also been shown to reduce HbA_{1c} levels in patients suboptimally controlled on either a sulfonylurea in the GetGoal-S trial [73] or a thiazolidinedione in the GetGoal-P trial [74]. In both of these 24-week trials, lixisenatide increased the proportion of patients achieving HbA_{1c} <7% (GetGoal-S 36.4% vs. 13.5%; GetGoal-P 52% vs. 26%, for lixisenatide and placebo, respectively; $P < 0.0001$) [73, 74].

Body Weight

In the studies of lixisenatide in combination with OADs, patients had a mean baseline body mass index (BMI) of ≥30 kg/m^2 (Table 2) and were offered diet and lifestyle counseling consistent with international or local guidelines for patients with T2DM, in addition to study medication. Lixisenatide was associated with a weight reduction of approximately 1 kg over the 24-week study periods when compared with placebo in GetGoal-F1 and GetGoal-S [73, 76]; smaller reductions in body weight were evident in other studies [72, 74]. In GetGoal-X, mean baseline body weight was slightly higher in the exenatide group (96.1 vs. 94.0 kg for lixisenatide), but mean BMI was similar (Table 2). In this study, body weight decreased from baseline in both groups: –2.96 kg with lixisenatide once daily and –3.98 kg with exenatide twice daily (LS mean difference 1.02 kg) [75]. As add-on to OADs, it is, therefore, clear that in patients with a high BMI, lixisenatide has beneficial effects on body weight.

Gastrointestinal and Other Adverse Events

Across these studies, lixisenatide was generally well tolerated. As monotherapy,

treatment-emergent AEs were comparable for lixisenatide and placebo (53.6% vs. 45.1%). There were no reports of suspected pancreatitis and no instances of lipase or amylase elevation as monotherapy [77]. AEs were also similar between lixisenatide and placebo as add-on to metformin in GetGoal-F1 (68%, 71%, and 66% lixisenatide one-step titration, two-step titration and placebo, respectively) and GetGoal-M (69.4% for the lixisenatide morning injection and 60% for placebo) [72, 76], as add-on to thiazolidinediones (72.4% and 72.7%) and as add-on to sulfonylureas with or without metformin (68.3% and 61.1%). In the latter study, one patient in the lixisenatide group died as a result of a cardiac event after 17 days' exposure to lixisenatide [73].

As monotherapy, 32.2% of lixisenatide-treated patients reported gastrointestinal AEs compared with 13.9% for placebo, with nausea being the most frequent (22.2% vs. 4.1%, respectively) [77]. The majority of these events were "mild to moderate" in intensity and resolved without the need for treatment [77]. As add-on to metformin in GetGoal-F1, gastrointestinal events were reported in a higher proportion of patients – 41.6%, 47.2%, and 21.9% for lixisenatide one-step titration, two-step titration and placebo, respectively [76], but were relatively lower in GetGoal-M as add-on to metformin, in which nausea and vomiting were reported in 22.7% and 9.4% for the lixisenatide morning injection and 7.6% and 2.9% for placebo, respectively [72]. Comparable gastrointestinal tolerability was evident in GetGoal-S (as add-on to sulfonylureas with or without metformin) with an incidence of 40.9% for lixisenatide and 20.0% for placebo [73]. As add-on to thiazolidinediones in GetGoal-P, rates for nausea, diarrhea, and vomiting were relatively low (23.5%, 7.1%, and 6.8% for lixisenatide vs. 10.6%, 10.6%, and 3.7% for placebo, respectively) [74]. Gastrointestinal tolerability also appeared better for lixisenatide compared with exenatide in GetGoal-X, in which nausea, vomiting, and diarrhea were reported in 24.5%, 10.1%, and 10.4% for lixisenatide and 35.1%, 13.3%, and 13.3% for exenatide, respectively (<0.05 for nausea) [75]. Therefore, across these studies, the incidence of gastrointestinal events with lixisenatide was of the order expected for available GLP-1 receptor agonists, and these events often resolve without the need for specific treatment. The effect of lixisenatide on heart rate has been evaluated in several studies. In a direct comparison between lixisenatide and liraglutide, lixisenatide treatment was associated with a heart rate reduction of 3.6 beats per min (bpm), whereas liraglutide administration resulted in an increase in heart rate of 5.3 bpm [52]. The ongoing Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA) study (ClinicalTrials.gov #NCT01147250) aims to evaluate the cardiovascular risk profile of lixisenatide in patients with T2DM who have recently experienced a cardiac event.

Hypoglycemia

Across the GetGoal studies, there was a low incidence of symptomatic hypoglycemia. As monotherapy, symptomatic hypoglycemia (defined as symptoms consistent with hypoglycemia, with accompanying blood glucose <3.3 mmol/L and/or prompt recovery with carbohydrate) were reported in four of 239 (1.7%) lixisenatide-treated patients and two of 122 (1.6%) patients receiving placebo [77]. As add-on to metformin, cases of symptomatic hypoglycemia were three of 161 (1.9%), four of 161 (2.5%), and one of 160 (0.6%) for lixisenatide one-step titration, two-step titration and placebo, respectively in GetGoal-FI [76], and 2.4% with a lixisenatide morning injection and 0.6% with placebo in GetGoal-M [72]. In GetGoal-S (as add-on to sulfonylureas with or without metformin), the incidence of symptomatic hypoglycemia was higher, as would be expected: 88 of 574 (15%) and 35 of 285 (12%)

for lixisenatide and placebo, respectively, and there was one case of severe hypoglycemia with lixisenatide [73]. As add-on to thiazolidinediones in GetGoal-P, symptomatic hypoglycemia was reported in 11 of 320 (3.4%) with lixisenatide and two of 159 (1.2%) with placebo [74]. In GetGoal-X, six-times fewer patients experienced hypoglycemic events (eight vs. 48 patients) and three-times fewer patients experienced symptomatic hypoglycemia (eight patients with lixisenatide vs. 25 patients with exenatide); there were no cases of severe hypoglycemia in either group [75]. These data accordingly confirm the low risk of hypoglycemia with lixisenatide, which may potentially be even lower than that associated with exenatide IR.

Lixisenatide in Combination with Basal Insulin

To investigate whether the pronounced reduction in postprandial glycemic excursions observed with lixisenatide could complement the fasting glucose control provided by basal insulin therapy, two randomized, placebo-controlled, 24-week trials and a third randomized, placebo-controlled trial with a 24-week treatment period followed by an extension phase of at least 52 weeks, have evaluated lixisenatide as add-on in patients suboptimally controlled on basal insulin for two of the studies (GetGoal-L and GetGoal-L-Asia) or on standard antidiabetic therapy in one study (GetGoal-Duo-1). In all of those studies, lixisenatide decreased both HbA_{1c} and prevented weight gain, or induced weight loss when compared with placebo [62, 70, 71].

Lixisenatide as Add-On to Basal Insulin and Metformin

The GetGoal-Duo-1 study was undertaken in patients suboptimally controlled on OADs. It consisted of a 12-week run-in period with introduction and titration of insulin glargine to a target FPG of 80–100 mg/dL and a 24-week treatment period during which 446 patients received either lixisenatide or placebo in combination with insulin glargine and metformin with or without a thiazolidinedione. Insulin glargine was also continuously titrated during this period. During the 12-week run-in period, the addition and titration of insulin glargine resulted in a decrease in HbA_{1c} of approximately 1%. The addition of lixisenatide led to a significantly greater HbA_{1c} decrease of 0.71% in the lixisenatide group compared with 0.40% in the placebo group (LS mean difference –0.32%; 95% confidence interval [CI] –0.46 to –0.17; $P < 0.0001$) (Fig. 4a) [71]. At the end of the 24-week treatment period, 56.3% of the lixisenatide patients achieved an HbA_{1c} of <7% compared with 38.5% in the placebo group [71]. Lixisenatide also improved 2-h PPG after a standardized breakfast (LS mean difference –3.16; 95% CI –3.95 to –2.37 mmol/L; $P < 0.0001$) (Fig. 4b). FPG increased moderately from baseline to week 24 for both lixisenatide and placebo (LS mean change from baseline 0.34 and 0.46 mmol/L, respectively; P = not significant).

Lixisenatide as Add-On to Basal Insulin With or Without Metformin

Comparable observations were seen in GetGoal-L, in which lixisenatide 20 µg once daily was added on in 495 patients with T2DM suboptimally controlled on a combination of basal insulin (mean previous insulin therapy, 55 U/day) with or without metformin [70]. When compared with placebo, lixisenatide reduced HbA_{1c}, the proportion of patients achieving HbA_{1c} <7% (28% vs. 12%, $P < 0.0001$) and 2-h PPG after a standardized breakfast (LS mean difference –3.81, 95% CI –4.70 to –2.93; $P < 0.0001$).

Lixisenatide as Add-On to Basal Insulin With or Without Sulfonylurea in Asian Patients

GetGoal-L-Asia evaluated the effect of lixisenatide in 311 Asian T2DM patients not achieving glycemic control with basal insulin with or without a sulfonylurea [62]. Similar to the other two studies of lixisenatide as add-on to basal insulin, the addition of lixisenatide 20 μg once daily improved HbA_{1c} (LS mean difference vs. placebo −0.88%; $P<0.0001$), the proportion of patients achieving HbA_{1c} <7% (35.6% vs. 5.2%) and ≤6.5% (17.8% vs. 1.3%) ($P < 0.0001$ vs. placebo), 2-h PPG and glucose excursion, and FPG.

Gastrointestinal and Other Adverse Events

Overall, AEs were similar for lixisenatide and placebo as add-on to basal insulin. In GetGoal-Duo-1, AEs were reported by 80% of lixisenatide-treated patients and 68% of placebo-treated patients [71]. In GetGoal-L, the incidence of AEs and serious AEs was reported to be 73.5% and 3.7% for lixisenatide and 68.3% and 4.2% for placebo [70]. No information is yet available about the incidence of cardiovascular events from these studies. In GetGoal-L-Asia, the frequency of serious treatment-emergent AEs was similar in the two groups: 6.5% in the lixisenatide group and 5.7% in the placebo group. However, two patients (1.3%) in the lixisenatide group experienced treatment-emergent AEs of cerebrovascular infarction (nonfatal ischemic stroke) [62].

The incidence of gastrointestinal events with lixisenatide in combination with basal insulin was similar to that observed in combination with OADs, although in Asian patients, the rate was slightly higher. In GetGoal-Duo-1, nausea, and vomiting were the most common gastrointestinal events (27.4% and 9.4% for lixisenatide vs. 4.9%

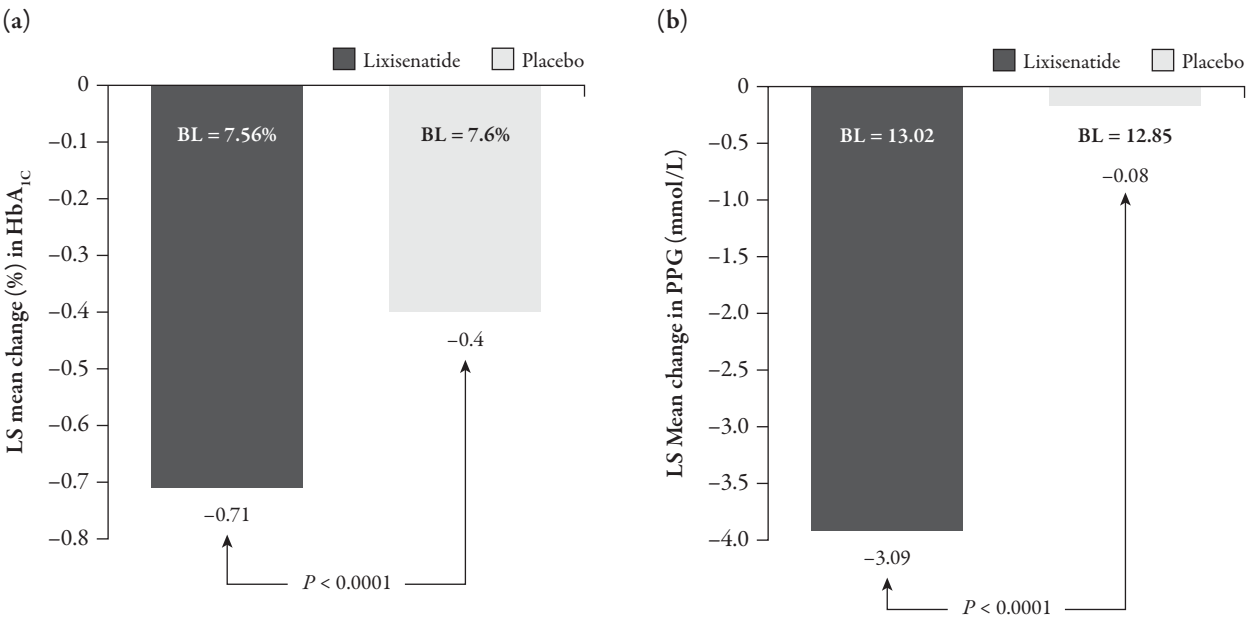

Fig. 4 Changes in (**a**) $HbA_{1c,}$ and (**b**) 2-h postprandial glucose after 24 weeks of treatment with lixisenatide 20 μg once daily or placebo as add-on to basal insulin glargine in patients ($n = 466$) with T2DM inadequately controlled on metformin with or without sulfonylurea with or without thiazolidinediones in the GetGoal-Duo-1 study. Lixisenatide reduced both HbA_{1c} and 2-h PPG versus placebo. *BL* baseline, *HbA_{1c}* glycated hemoglobin, *LS* least squares, *PPG* postprandial plasma glucose, *T2DM* type 2 diabetes mellitus

and 1.3% for placebo, respectively) [71]. In GetGoal-L, nausea, vomiting, and diarrhea were reported in 26.2%, 8.2%, and 7.3% of patients receiving lixisenatide and 8.4%, 0.6%, and 5.4% of patients receiving placebo, respectively [70]. In GetGoal-L-Asia, rates for nausea and vomiting were 39.6% and 18.2% versus 4.5% and 1.9% for lixisenatide and placebo, respectively [62]. Accordingly, as add-on treatment to basal insulin, these data indicate that lixisenatide has a good overall tolerability profile, with nausea being the most common gastrointestinal AE.

Hypoglycemia

The incidence of symptomatic hypoglycemia was similar to, or only slightly increased, over placebo across these studies. As expected, in patients receiving sulfonylureas, the incidence of symptomatic hypoglycemia was higher than in those not treated with these drugs. In GetGoal-Duo-1, a total of 22.4% of patients experienced symptomatic hypoglycemia with lixisenatide versus 13.5% for placebo [71]. In GetGoal-L, the incidence of symptomatic hypoglycemia was similar between groups (27.7% for lixisenatide vs. 21.6% for placebo), but four cases of severe hypoglycemia occurred in the lixisenatide group [70]. In GetGoal-L-Asia, the incidence of symptomatic hypoglycemia was more frequent with lixisenatide versus placebo (42.9% vs. 23.6%), but in patients not receiving sulfonylureas, the incidence was similar between groups (32.6% vs. 28.3%) [62].

Effect of Lixisenatide on Body Weight

As add-on to basal insulin, lixisenatide had a beneficial effect on body weight. In GetGoal-Duo-1, body weight increased by 1.2 kg in the placebo group and 0.3 kg in the lixisenatide group (LS mean difference –0.9 kg; $P = 0.0012$) [71]. In GetGoal-L, body weight decreased by 1.80 kg in the lixisenatide group and 0.52 kg in the placebo group (LS mean difference –1.28 kg; $P < 0.0001$) [70]. In GetGoal-L-Asia, the cohort had a lower baseline BMI (Table 2), but there was still a trend towards weight loss with lixisenatide compared with placebo (LS mean change –0.38 vs. +0.06 kg, respectively; P = not significant) [62].

Lixisenatide in Specific Patient Populations

A subanalysis of 379 patients aged ≥65 years (including 48 patients aged ≥75 years) from the GetGoal program has demonstrated that the efficacy and safety of lixisenatide, including hypoglycemia and gastrointestinal events, was similar regardless of age, with comparable decreases in HbA_{1c} in those ≥65 years of age and ≥75 years of age, and greater decreases versus placebo in both age categories [78]. Data in patients with renal, cardiac, or hepatic failure are hitherto limited. In individuals without diabetes, mild to moderate renal impairment did not appear to affect the pharmacokinetics or safety of lixisenatide (5 µg dose). In individuals with severe renal impairment, drug exposure was increased, suggesting that dose adjustment may be required in this population [79]. A large randomized, controlled study (ELIXA) to evaluate the effects of lixisenatide in patients with T2DM who have recently experienced an acute coronary syndrome event is currently underway.

CONCLUSIONS

Lixisenatide is a novel "short-acting" once-daily prandial GLP-1 receptor agonist that in pharmacokinetic and pharmacodynamic studies has been demonstrated to restore the first and second-phase insulin responses, accelerate glucose disposition, and slow gastric emptying. Despite its relatively short half-life, lixisenatide is suitable for once-daily dosing, at least partly reflecting its marked ability to delay gastric emptying [68].

Lixisenatide once daily has undergone extensive clinical evaluation in the phase 3 trial program, GetGoal. These clinical data have demonstrated that lixisenatide is generally well tolerated in patients with T2DM, with possibly better gastrointestinal tolerability and a lower risk of hypoglycemia than exenatide IR [75]. As with other GLP-1 receptor agonists, lixisenatide reduces HbA_{1c}, but unlike liraglutide and exenatide LAR, has particular efficacy to minimize postprandial glucose excursions. The efficacy of lixisenatide in glucose-lowering (HbA_{1c}) has been demonstrated as monotherapy, in combination with OADs, and in combination with basal insulin. In the direct comparison with exenatide IR as add-on to metformin, lixisenatide demonstrated noninferior efficacy in reducing HbA_{1c} [75].

The use of GLP-1 receptor agonists, such as lixisenatide, in combination with basal insulin is of particular interest and is likely to represent an important therapeutic advance for patients with T2DM, providing improvements in glycemic control while reducing body weight or preventing weight gain, without increasing the risk of hypoglycemia. In all three GetGoal studies as add-on to basal insulin, lixisenatide resulted in significant additional improvements in HbA_{1c} and postprandial glucose control versus placebo, as well as a beneficial effect on body weight.

One of the most interesting effects of GLP-1 is its ability to slow gastric emptying, particularly as the pivotal role of the rate of gastric emptying in postprandial glycemic control is now appreciated. It appears that the longer-acting GLP-1 receptor agonists, liraglutide and exenatide LAR, are subject to tachyphylaxis for their initial effect to slow gastric emptying as a result of more sustained receptor activation, while the effect of short-acting agents is sustained and substantial. In line with this, lixisenatide has been demonstrated to slow gastric emptying after administration for 4 weeks [68], and it is likely that the pronounced effect of lixisenatide on PPG is mediated, at least partly, by the reduction in gastric emptying. In a direct comparison with liraglutide, lixisenatide reduced PPG excursions much more than the long-acting agent [52]. Although once-daily administration of lixisenatide in the morning reduces glycemia throughout the day, the greatest glucose-lowering effect appears to occur with the first meal, and it would be of interest to determine the comparative effects of lixisenatide on glycemia when administered with the main meal, as opposed to breakfast.

As data emerge from the GetGoal program, it is clear that lixisenatide will represent an important addition to the options currently available for the management of T2DM, with a particular advantage over exenatide IR of once-daily administration. Lixisenatide is likely to prove to be an excellent therapeutic choice in those T2DM patients who have relatively faster gastric emptying and, because of its pronounced impact on PPG, in patients with relatively lower HbA_{1c}, including those already receiving basal insulin.

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