Incretin Mimetics as Emerging Treatments for Type 2 Diabetes

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OBJECTIVE: To review the physiology, pharmacology, and clinical efficacy of glucagon-like peptide (GLP-1) and the incretin mimetics exenatide and liraglutide in clinical studies.

DATA SOURCES: Primary literature obtained via MEDLINE (1966–April 2004) and *International Pharmaceutical Abstracts* (1970–April 2004) searches; abstracts obtained from meeting sources and manufacturers.

STUDY SELECTION AND DATA EXTRACTION: All English-language studies and abstracts evaluating GLP-1, exenatide, and liraglutide in the treatment of patients with type 2 diabetes were reviewed. Data from animal studies were also included if human data were not available. Primary and review articles related to the physiology, development, and evaluation of GLP-1s were reviewed.

DATA SYNTHESIS: GLP-1, exenatide (exendin-4, AC2993), and liraglutide (NN2211) are incretin mimetics that have been shown in human studies to be an effective treatment to improve glycemic control in patients with type 2 diabetes. Mechanisms by which these compounds improve glycemic control include enhancing glucose-dependent pancreatic secretion of insulin in response to nutrient intake, inhibiting glucagon secretion, delaying gastric emptying, and promoting early satiety. GLP-1 has been shown to promote pancreatic progenitor cell differentiation and improve β-cell function and lifespan. Reported adverse effects of exenatide and liraglutide include nausea, vomiting, and transient headache, as well as increased risk of hypoglycemia when used with sulfonylureas.

CONCLUSIONS: Clinical studies show that GLP-1, exenatide, and liraglutide improve glycemic control for patients with type 2 diabetes through unique mechanisms not available with current pharmaceutical products. Ongoing Phase III studies will help to further position these compounds as treatment options for patients with type 2 diabetes.

KEY WORDS: exenatide, glucagon-like peptides, incretin mimetics, liraglutide, type 2 diabetes.

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Currently, 18.2 million Americans have type 2 diabetes, and treatment consists of lifestyle modifications, oral hypoglycemic agents (sulfonylureas, biguanides, acarbose, thiazolidinediones), and/or insulin therapy.[1] Unresponsiveness to oral antihyperglycemic agents is high: after 5–7 years of therapy with sulfonylureas, 50% of these patients will require insulin therapy.[2] β-Cell dysfunction leads to decreased insulin secretion and resulting hyperglycemia.[3] An emerging area of study involves the enteroinsular axis, a process by which peptides (gut hormones, incretin hormones) are secreted by intestinal cells in response to food intake to affect pancreatic insulin secretion. This article reviews the available data on the naturally occurring incretin hormone glucagon-like peptide (GLP-1) and similar incretin mimetics in Phase III studies (exenatide, liraglutide), with emphasis on the physiology, pharmacokinetics, efficacy, and safety of these compounds and their emerging role in the treatment of patients with type 2 diabetes.

Data Sources

MEDLINE (1966–April 2004) and *International Pharmaceutical Abstracts* searches (1970–April 2004) were conducted for English-language articles using the terms glucagon-like peptides, incretin mimetics, exendin-4, AC2993, exenatide, NN2211, and liraglutide. Articles relevant to the physiology, pharmacology, and efficacy in published clini-

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Physiology of Incretin Hormones

Incretin hormones are peptides released from cells in the gastrointestinal tract in response to a nutrient stimulus, leading to glucose-dependent insulin release from the pancreas.[4] GLP-1 is a naturally occurring incretin hormone in humans derived from the proglucagon gene. In mammals, the proglucagon RNA transcript (Figure 1) is translated and processed differently in pancreatic islet cells and intestinal cells.[5,6] The α cells of the pancreas have prohormone convertase 2 that converts proglucagon into functional glucagon, and intestinal L cells of the jejunum and ileum process proglucagon into GLP-1.[7-9] Glucagon is the counterregulatory hormone of insulin, raising plasma levels of glucose in response to insulin-induced hypoglycemia by enhancing glycogenolysis and gluconeogenesis.[10] The 2 forms of GLP-1 secreted after meal ingestion are GLP-1 (7-37)amide and GLP-1 (7-36)amide, which differ by a single amino acid.[11] Approximately 80% of circulating active GLP-1 is in the form of GLP-1 (7-36)amide.[12] These 2 hormones have identical half-lives, equal potency, and similar biological activities.[13] GLP-1 acts by binding to a G-protein–linked receptor expressed on islet β cells.[14]

No reports exist of genetic mutations in patients with type 2 diabetes or evidence that patients with maturity-onset diabetes of the young have a genetic linkage to defects of the GLP-1 receptor gene.[15] In patients with type 2 diabetes or impaired glucose tolerance, there are modest but significant reductions in meal-stimulated circulating levels of GLP-1.[16-18] GLP-1 is rapidly secreted by the L cells of the intestine in response to food ingestion in humans, by both neural and hormonal signaling initiated by exposing the proximal gastrointestinal tract to ingested nutrients, as well as by subsequent direct contact of those nutrients as they are exposed to the L cells in the distal jejunum and ileum, particularly in response to a mixed meal or a meal high in fat and complex carbohydrates.[11,19,20] Release of GLP-1 has been shown to potentiate glucose-dependent insulin secretion by stimulating β-cell growth and differentiation and insulin gene expression.[21-24] GLP-1 has been shown to inhibit β-cell death in human islets cultured in vitro.[23,25] The mechanism of this action has been shown in rodent models to involve GLP-1 inducing expression of the homeodomain transcription factor islet duodenum homeobox-1 (IDX-1), a master regulator of pancreas development and β-cell function, inducing progenitor cells found in the pancreatic ducts to develop into β-cells.[24,26,27] These pancreatic progenitor cells have been isolated from humans, and proof of concept that these cells reside within human pancreatic ducts has been completed.[28] These data suggest that GLP-1 can improve β-cell differentiation, increase β-cell mass, and increase β-cell lifespan. Other effects of GLP-1 have been shown to inhibit glucagon secretion, delay gastric emptying, and act through the central nervous system to decrease appetite, increase sensation of satiety, and promote weight loss.[29-33]

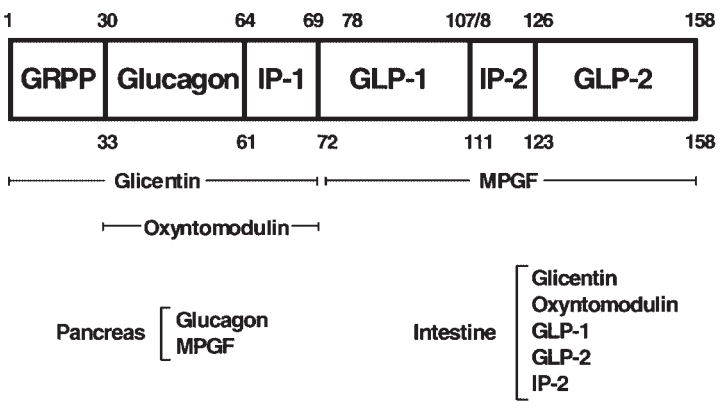

Figure 1. Proglucagon mRNA transcript. Copyright 2003, The Endocrine Society.[5] GLP = glucagon-like peptide; GRPP = glicentin-related pancreatic polypeptide; IP = intervening

Pharmacology of GLP-1

GLP-1 is inactivated rapidly by dipeptidyl peptidase IV (DPP-IV) in plasma by cleaving the penultimate alanine residue to generate GLP-1 (9-36)amide, with the half-life of intact GLP-1 in vivo <2 minutes.[34,35] A study of healthy volunteers receiving subcutaneous GLP-1 (7-36) amide showed a dose-related increase of GLP-1 plasma concentrations, and after an intravenous glucose bolus, more than in the basal state, GLP-1 augmented the insulin secretory response and suppressed plasma glucagon.[36] A study of healthy patients given an intravenous infusion of GLP-1 during ingestion of a meal showed that GLP-1 increased and augmented the dose–response relationship between glucose concentration and insulin secretion.[37] The effect of GLP-1 on glucose control appears to be a function of enhanced, glucose-dependent insulin secretion and not improved peripheral insulin resistance.[38,39] Comparing acute administration of GLP-1 with a 3-hour infusion of GLP-1 in diabetic and nondiabetic patients showed that both groups had improved insulin secretion, but only the 3-hour infusion led to augmented improvement in first-phase insulin response.[40] Comparison of 16- and 24-hour infusions of GLP-1 showed that the most efficacious dosing based on nocturnal and fasting plasma glucose levels was in the 24-hour continuous infusion group.[41] Evaluation of GLP-1 (7-36) given by a single buccal tablet showed that therapeutic plasma levels of GLP-1 in healthy humans were achieved, consistent with a relative bioavailability of 7% versus intravenous injection and 47% versus subcutaneous injection.[42]

The clinical applicability of GLP-1 therefore is limited in humans, as the insulin-secreting effects of GLP-1 are best observed with continuous infusion and that GLP-1 is rapidly degraded by DPP-IV.

Exenatide

Exenatide is a naturally occurring 39-amino acid GLP-1 agonist isolated from the salivary

tum (Gila monster).[43] This peptide has 53% amino acid similarity to mammalian GLP-1, effectively binds to the GLP-1 receptor, and is highly resistant to DPP-IV.[44] Compared with GLP-1, exenatide has up to 3000-fold greater potency for glucose-lowering in vivo and is a more potent stimulator of glucose-dependent insulin release when given intravenously.[45-47] Infusion of exenatide and GLP-1 in animal models has replicated a bell- shaped dose response for both compounds, with exenatide demonstrating a greater maximal effect than GLP-1.[48] Phase I clinical trials have shown that subcutaneous exenatide was generally well tolerated at doses of ≤0.1 µg/kg, with nausea and vomiting being dose-limited at 0.3 µg/kg, and all exenatide doses increased plasma insulin.[49] Exenatide suppresses glucagon secretion, slows gastric emptying, reduces food intake, and promotes β-cell proliferation and neogenesis from precursor cells. Exenatide does not acutely enhance insulin activity in nondiabetic humans and, unlike GLP-1, does not suppress gastric acid secretion.[39,50-54]

Phase II trials with exenatide in 323 patients with type 2 diabetes identified an optimal glucose-lowering subcutaneous dose range of 0.05–0.2 µg/kg.[55] Transient nausea and vomiting were dose-limiting adverse events, with this nausea mitigated by a dose initiation period of one month at 5 µg twice daily followed by a maintenance dose of 10 µg twice daily.[56]

PHARMACOKINETICS

Exenatide was administered to rats for the purpose of investigating the pharmacokinetics after intravenous, subcutaneous, and intraperitoneal administration, and showed dose-dependent increases in plasma concentration, regardless of administration route.[57] Exenatide plasma levels exhibited a gradual single-phase decay, occurring 30 minutes after injection of all doses. Clearance of exenatide from plasma was 4−8 mL/min and was primarily cleared via a renal route.

Table 1 describes the pharmacokinetics of exenatide in humans.[58,59] Exenatide demonstrated first-order pharmacokinetics, with the concentration decreasing in a logarithmic fashion over time and plasma concentrations detectable 6 hours after the injection. The volume of distribution following intravenous infusions to healthy volunteers was 64 ± 7 mL/kg, suggesting that exenatide is not likely to be highly tissue bound. Exenatide is renally cleared, with a documented clearance rate of 1.8 ± 0.2 mL/kg/min.

CLINICAL EFFICACY

Several clinically relevant trials have documented the beneficial effects of exenatide (Table 2[51,58-61]). A randomized, double-blind, single-dose crossover study in healthy individuals was performed.[58] Subjects received either for a total of 6 hours on day 1, returning in one week to receive another infusion in a double-blind fashion after an 8-hour fast. A standard breakfast was given one hour after start of infusion, and 3 hours later, the subjects were given a free-choice lunch buffet. Food quantities were weighed before and after participants ate lunch, and feelings of fullness were rated.

No patients experienced adverse events from the infusion. In the fasting state in the first hour, fasting plasma glucose levels fell significantly from 81 to 72 mg/dL ($p < 0.005$), with no change in the placebo group. There was no significant change in the 3-hour postprandial glucose level, although the peak postprandial glucose level (glucose excursion) was lower in the exenatide group and gastric emptying time was decreased. Food intake was 19% lower in the exenatide group (208 calories) at the buffet lunch compared with the placebo group, and the effect appeared to carry over to the evening meal. Noting this small decrease in absolute caloric intake, subjects reported no difference in feelings of fullness or nausea.[58]

Protocols to study the effects of exenatide in both a hyperglycemic and fluctuating state of blood glucose concentrations were performed in patients with type 2 diabetes and healthy volunteers.[60] To reproduce a hyperglycemic state in patients with diabetes, diabetic medications were withheld for 3 days before the study period. A hyperglycemic clamp (continuous glucose infusion) that raised subjects' blood glucose levels by approximately 100 mg/dL from the fasting state for 5 continuous hours was used to measure changes in insulin release. An exenatide infusion was then given for one hour, and a standard meal was given 5.5 hours later. A second protocol allowed the hyperglycemic clamp to be stopped in the third hour to allow plasma glucose to fall to fasting levels, then increased again by 100 mg/dL during the fifth and final hours to determine the level of glucose dependency of exenatide.

The results from the first protocol revealed that insulin release was potentiated during and in the hours following the exenatide infusion. Results from the second protocol showed that, when the fasting state was resumed, insulin levels fell, but when plasma glucose was raised again, plasma insulin levels were potentiated to an even greater de-

Table 1. Pharmacokinetic Parameters of Exenatide

Parameter	Edwards et al. (2001)[58]	Fineman et al. (2003)[59]
Dose/route	0.05 pmol/kg/min intravenous	0.08 µg/kg sc
C_{max}[a]	16.4 ± 0.9 pmol/L	163 ± 86 pg/mL (day 1) 159 ± 81 pg/mL (day 28)
$t_{1/2}$ (min)[a]	26 ± 3	202 ± 182 (day 1) 226 ± 170 (day 28)
Cl (mL/min•kg)[a]	1.8 ± 0.2	NR
V_d (mL/kg)[a]	64 ± 7	NR
t_{max} (h)	2–3	NR

C_{max} = peak plasma concentration; Cl = clearance; NR = not reported; $t_{1/2}$ = half-life; t_{max} = time to maximum plasma concentration; V_d = volume of distribution.
[a]Mean ± SEM

gree than during the initial phase. The results demonstrated a glucose-dependent insulinotropic effect from exenatide, suggesting an amplification of β-cell insulin release when glucose concentrations were above the normal range, but not when glucose concentrations were below or within the normal range.[60]

To evaluate the effect of multiple doses of exenatide over a one-month period, a study of 9 patients with type 2 diabetes (mean age 57 y, mean body mass index [BMI] 33 kg/m², mean glycosylated hemoglobin [HbA_{1c}] 9.1%) not being treated with insulin was performed.[61] Oral diabetic agents were stopped a week prior to the study, and patients were placed on hyperglycemic and hyperinsulinemic euglycemic clamps. Subcutaneous injections of exenatide at an initial dose of 12 pmol/kg were titrated weekly to a maximum of 96 pmol/kg (0.4 µg/kg). Exenatide was continued for one month, and patients were instructed to monitor their blood glucose levels at least 8 times a day (before and 1 hour after every meal as well as before and after the exenatide injection). Hyperglycemic and hyperinsulinemic euglycemic clamps were repeated at the end of the study.

Results showed that exenatide reduced HbA_{1c} (9.1% vs 8.3%; $p = 0.009$) and lowered glucose one hour after breakfast ($p < 0.0001$) after twice-daily dosing. No difference was noted in glucose response, plasma insulin levels, or glucagon after a month of exenatide compared with before treatment. However, C-peptide levels were significantly higher during the clamp. A favorable response to adipose tissue sensitivity to insulin was noted, with nonesterified free fatty acid levels higher after exenatide treatment, and no desensitization to the effects of exenatide over the course of the month were observed.[61]

Kolterman et al.[51] published a trial that included 2 substudies of exenatide use in patients with type 2 diabetes. The aim of study A was to investigate postprandial glucose response, and study B evaluated the effect on fasting plasma glucose levels. In study A, patients with type 2 diabetes (mean age 56 y, mean BMI 29 kg/m², mean HbA_{1c} ≤12%, fasting plasma glucose <260 mg/dL) were divided into groups based on their baseline diabetes therapy: (1) diet management alone, (2) oral therapy with HbA_{1c} <8%, (3) oral therapy with HbA_{1c} 8–12%, or (4) insulin treated. Subjects were randomly given a dose of exenatide 0.1 µg/kg or placebo subcutaneously twice a day for 5 days, then switched to the other arm after a 2- to 3-day washout period. Patients were given a standardized liquid breakfast 10 minutes after their morning injection, and postprandial information was recorded. A dose of acetaminophen was given to measure gastric emptying.

The authors observed that postprandial glucose levels were significantly lower over the 5 hours after the standard meal for the exenatide group versus placebo, with no difference between day 1 or day 5, nor between any of the predefined patient groups. Plasma glucose levels in the exenatide group were lower in the hours after the meal (from 160 to 126 mg/dL at 3 h), compared with placebo where it

Table 2. Summary of Clinical Trials with Exenatide and Liraglutide

Reference	Pts.	Treatment	Dose	Significant Clinical Response
Exenatide				
Edwards et al. (2001)[58]	healthy non-diabetics (n = 8)	single 6-h infusion	0.05 pmol/kg/min	lower FBG, lower glucose excursion, reduced food intake
Egan et al. (2002)[60]				
protocol 1	healthy non-diabetics (n = 7)	single 1-h infusion	0.15–0.59 pmol/kg/min	overall insulin release potentiated after infusion
protocol 2	non–insulin-treated type 2 diabetics (n = 7)	single 1-h infusion	0.15–0.59 pmol/kg/min	insulin release amplified when glucose levels above normal
Egan et al. (2003)[61]	non–insulin-treated type 2 diabetics (n = 9)	1 mo, once or twice daily sc injections	12–96 pmol/kg (0.05–0.4 µg/kg)	lower HbA_{1c}, FPG, and 1-h PPPG; elevated C-peptide, NEFA levels
Kolterman et al. (2003)[51]				
study A	type 2 diabetics (n = 24)	5 days, twice-daily sc injections	0.1 µg/kg	lower PPPG, postprandial insulin, delayed gastric emptying
study B	type 2 diabetics (n = 13)	single-dose sc injections	0.05, 0.1, 0.2 µg/kg	lower FPG, increased insulin levels at 3 h, no clinical differences among the 3 doses in glycemic control
Fineman et al. (2003)[59]	type 2 diabetics (n = 109)	28 days, 2 or 3 times a day sc injections	0.08 µg/kg	lower fructosamine, HbA_{1c}, PPPG; increased β-cell function
Liraglutide				
Juhl et al. (2002)[66]	type 2 diabetics (n = 11)	single sc dose	10 µg/kg	lower FPG and premeal glucose; lower glucose exposure and excursion; increased insulin levels and delayed gastric emptying
Chang et al. (2003)[65]	type 2 diabetics (n = 10)	single sc dose	7.5 µg/kg	increased insulin levels in response to elevated glucose levels

FPG = fasting plasma glucose; HbA_{1c} = glycosylated hemoglobin; NEFA = nonesterified free fatty acid; PPPG = postprandial plasma glucose

increased (from 170 to 289 mg/dL). Use of postprandial insulin was significantly lower in the exenatide group, with similar results found on days 1 and 5. Glucagon levels did not change from baseline in the exenatide group, but increased in the placebo group after the meal. Gastric emptying was delayed, as measured by postprandial plasma acetaminophen concentrations, which showed much reduced levels for the first 3 hours; peak concentrations at 5 hours were not different.[51]

Study B was a randomized, double-blind, placebo-controlled, 4-period crossover trial of patients with type 2 diabetes receiving only oral therapy for diabetes (mean age 49 y, mean BMI 33 kg/m²).[51] In 4 random sequences, subjects were given subcutaneous placebo or exenatide 0.05, 0.1, or 0.2 µg/kg as single doses each evening before a study day. All doses of exenatide reduced fasting plasma glucose significantly compared with placebo; no dose was found to be significantly better. The nadir of the plasma glucose occurred 3 hours after the dose given the night before, although it was still significantly lower at 8 hours. A dose-dependent rise in plasma insulin levels for the first 3 hours after the dose was observed, and by 8 hours, insulin levels were similar to those of placebo. No differences in glucagon levels were noted compared with placebo, although the authors noted a trend toward suppression in the exenatide groups. Mild adverse effects included headache, nausea, and vomiting; no subjects withdrew because of adverse effects.

A multicenter, triple-blind, randomized, parallel, placebo-controlled study examining the effects of exenatide in combination with existing oral drug therapy for diabetes was performed.[59] Patients (mean age 52 y, mean HbA_{1c} 9.2%, mean BMI 33 kg/m²) were taking either a sulfonylurea, metformin, or both at stable doses for at least 6 months prior to enrolling in the study and continued these medications throughout the study. Patients were assigned to 1 of 4 groups for a treatment period of 28 days: placebo or exenatide 0.08 µg/kg at breakfast and supper, or at breakfast and bedtime, or 3 times a day (all pts. received subcutaneous injections 3 times a day, with placebo used as needed to maintain assigned group). Measurements of fructosamine, HbA_{1c}, body weight, lipids, and other parameters were performed at baseline and day 28; fasting and postprandial glucose (after a standardized meal) were obtained at these times and also on day 14.

The results showed that fructosamine was significantly reduced in the exenatide groups compared with placebo ($p < 0.004$). HbA_{1c} was also significantly reduced compared with placebo, with an overall mean reduction of 0.9% across the treatment groups ($p < 0.006$). β-Cell function, as calculated by the homeostasis model analysis, was 50–100% greater in the exenatide groups compared with placebo ($p < 0.05$). Postprandial glucose levels were significantly lower in the exenatide groups versus placebo, observed on the first day of therapy and maintained until day 28 ($p < 0.004$). Fasting plasma glucose was not significantly different compared with placebo at day 28. There were no differences between the various exenatide regimens for any of these parameters, logic parameters, or cortisol were observed. About 20% of patients treated with exenatide developed low-titer antibodies with no effect on therapeutic results. Mild to moderate nausea developed in 31% of exenatide patients, most occurring in the initial days of therapy; only 4 patients withdrew from the study due to nausea, and only 13% had persistent nausea for the entire treatment period. Fifteen percent of patients experienced hypoglycemia, occurring only in those taking concurrent sulfonylurea therapy with exenatide.[59]

Liraglutide

Liraglutide (NN2211) is a synthetic acylated derivative of GLP-1 that has agonist activity at GLP-1 receptors being developed for once-daily subcutaneous injection. The prolonged effects of liraglutide are obtained by attaching a fatty acid molecule at one position of the GLP-1 molecule that allows for binding to albumin and a slow release from the reservoir. Subcutaneous dosing of liraglutide has been shown in animal models to reduce food intake and body weight, increase insulin secretion, inhibit glucagon secretion, decrease gastric emptying, reduce blood glucose in a dose-dependent manner, and increase the proportion of pancreatic β-cells in mice.[62-64]

Single doses of liraglutide administered to human subjects with type 2 diabetes have shown significant increases in insulin and C-peptide levels in a glucose-dependent manner compared with placebo, and liraglutide administered at bedtime significantly lowered fasting and postprandial glucose, suppressed glucagon secretion, and delayed gastric emptying.[65,66]

PHARMACOKINETICS

Studies with healthy men to investigate the pharmacokinetics, safety, tolerability, and pharmacodynamics of liraglutide when administered in single doses by the subcutaneous and intravenous routes were performed.[66,67] Table 3 documents the pharmacokinetic results from subjects administered 5 µg/kg intravenously and 10 µg/kg subcutaneously. A subcutaneous dose of 10 µg/kg administered at bedtime had a half-life of 10 hours and a time to maximum concentration of 12 hours, suggesting that bedtime dosing should provide for maximum plasma concentrations to occur during the day.[66] The absolute bioavailability of liraglutide was determined to be 55%.[67]

A single-center, randomized, double-blind, placebo-controlled, parallel-group dose-escalation study in healthy men (n = 30) was conducted, with data analyzed on day 1 to determine single-dose kinetics and after days 5–11 to determine multiple-dose kinetics. Pharmacokinetic data for subjects administered liraglutide 10 µg/kg are summarized in Table 3.[68]

CLINICAL EFFICACY

Published clinical studies of liraglutide are summarized

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