

# Pharmacokinetics and Pharmacodynamics of Liraglutide, a Long-Acting, Potent Glucagon-Like Peptide-1 Analog

Jerry Meece, B.S., FACA

Despite the continued development of new pharmacologic agents, and the use of several existing drug therapies, almost two thirds of patients with type 2 diabetes mellitus do not reach the American Diabetes Association–targeted hemoglobin A<sub>1c</sub> level of less than 7.0%. Therefore, maintaining adequate metabolic control remains a primary concern for many clinicians and patients. It is now well recognized that in addition to defective secretion and action of insulin, other hormones also potentially play a role in the development and progression of type 2 diabetes. Glucagon-like peptide-1 (GLP-1) is a gastrointestinal hormone from the incretin family, which stimulates insulin secretion and plays an important role in regulating the enteroinsular axis. Incretin-based therapies are the newest class of glucose-lowering drugs for the treatment of type 2 diabetes and may help address some of the unmet needs in this therapeutic area. Liraglutide is a once-daily GLP-1 analog that has been recently approved by the European Union regulatory agency and is in late-stage review by the United States Food and Drug Administration for the treatment of type 2 diabetes. The pharmacokinetic and pharmacodynamic properties of liraglutide and mechanisms behind its protracted action, which in turn enables enhanced glycemic control, are reviewed.

**Key Words:** type 2 diabetes mellitus, liraglutide, GLP-1 analogs, incretins, pharmacokinetics, pharmacodynamics.

(Pharmacotherapy 2009;29(12 Pt 2):33S–42S)

Diabetes mellitus is a major global health problem that affected an estimated 246 million individuals worldwide in 2007 and is projected to reach 380 million by 2025.<sup>1</sup> In the United States, 23.6 million adults (~8% of the population) have been diagnosed with diabetes, of which 90–95% were found to have type 2 diabetes.<sup>2,3</sup>

Progressive decline of  $\beta$ -cell function, together with an increase in the demand for insulin as tissues become insulin resistant, contributes to the pathophysiology of hyperglycemia in type 2 diabetes.<sup>4</sup> During the time of diagnosis of type 2

diabetes, patients may have already lost almost 50% of  $\beta$ -cell function, and as the disease progresses, further deterioration of  $\beta$ -cell function is observed; in such instances, monotherapy with one oral agent is insufficient.<sup>5</sup> The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that after 3 years of monotherapy, approximately 50% of the patients were able to maintain hemoglobin A<sub>1c</sub> (A1C) levels below 7.0%, and after 9 years of monotherapy, only 25% maintained the same level of glycemic control.<sup>6</sup> Typically, in type 2 diabetes, the patient progresses from dietary modifications and exercise to monotherapy and then to combination therapy. During this process there are bound to be periods of inadequate glycemic control, which can contribute to micro- and macrovascular complications in the long term. Thus, newer drug therapies are needed to

---

From the Plaza Pharmacy and Wellness Center, Gainesville, Texas.

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For questions or comments, contact Jerry Meece, B.S., FACA, C.D.E., Plaza Pharmacy and Wellness Center, 411 North Grand Avenue, Gainesville, TX 76240-4323; e-mail: [jmeece12@cooke.net](mailto:jmeece12@cooke.net).



In a dose-finding study in 24 healthy Japanese men who received three consecutive dose levels of liraglutide (15–25 µg/kg), the daily pharmacokinetic profiles after receiving the last dose showed dose-dependent increases in area under the concentration-time curve from 0–24 hours ( $AUC_{0-24}$ ), maximum concentration ( $C_{max}$ ), and minimum concentration ( $C_{min}$ ).<sup>32</sup> However, elimination rate constant, volume of distribution, and clearance were not affected by dose. The median  $T_{max}$  in the 15-, 20- and 25-µg/kg groups was 7.0, 8.0, and 7.0 hours, respectively.

Age and sex pharmacokinetic equivalence of subcutaneous liraglutide 1 mg once/day demonstrated that when adjusted for body weight, equivalence was declared for  $AUC_{0-t}$  between young and elderly subjects, and no significant effect of sex was observed.<sup>33</sup> Liraglutide was shown to be slowly absorbed, with a  $T_{max}$  of 11–13 hours and half-life of 12–14 hours.

In patients with type 2 diabetes, pharmacokinetic properties of subcutaneous liraglutide 6 µg/kg once/day were evaluated using 24-hour plasma profiles. The mean half-life observed at steady state was 17.9 hours, whereas mean  $\pm$  SD  $T_{max}$  was  $10.1 \pm 3$  hours.<sup>34</sup> In another study in patients with type 2 diabetes, pharmacokinetic properties of liraglutide, administered as a single, subcutaneous dose of 10 µg/kg, were evaluated by 11-point profiles for up to 63 hours after dosing.<sup>35</sup> Liraglutide was detected 60 minutes after injection, with a mean  $\pm$  SD half-life of  $10 \pm 4$  hours and  $T_{max}$  of  $12 \pm 2$  hours.

After injection of a single, subcutaneous dose of liraglutide 0.75 mg, comparison using 72-hour blood sampling between subjects with normal renal function and those with severe renal impairment did not show equivalence.<sup>36</sup> A regression analysis failed to show a significant effect of decreasing creatinine clearance on the AUC of liraglutide. A meta-analysis of six phase III Liraglutide Effect and Action in Diabetes (LEAD) studies was performed to assess the efficacy and safety of liraglutide in patients with mild renal impairment.<sup>37</sup> Compared with the general study population, no change in serum creatinine concentration was observed in patients with mild renal impairment who were administered liraglutide 1.8 or 1.2 mg. As discussed earlier, the structural modifications of liraglutide result in the drug not being excreted in urine, and its pharmacokinetic properties remain unchanged in patients with varying degrees of renal impairment. In contrast, exenatide is

predominantly eliminated by glomerular filtration, and thus it is not recommended in patients with severe renal impairment or end-stage renal disease.

To evaluate the effect of hepatic impairment on the pharmacokinetic properties of liraglutide, six patients with normal hepatic function and 18 patients with mild, moderate, or severe hepatic impairment received a single dose of subcutaneous liraglutide 0.75 mg.<sup>38</sup> Pharmacokinetic profiles assessed 72 hours after dosing revealed hepatic impairment:normal AUC ratios of 0.77, 0.87, and 0.56 for mild, moderate and severe impairment, respectively. Liraglutide exposure appeared to decrease with an increasing degree of hepatic impairment, with no significant differences in the safety parameters between the two groups. It was concluded that patients with type 2 diabetes and renal insufficiency or hepatic impairment do not require liraglutide dosage adjustments.

The effect of injection site (abdomen, upper arm, and thigh) on the pharmacokinetic profile of liraglutide was investigated. It was found that based on the AUC, abdomen and thigh were equivalent.<sup>39</sup> However, lower bioavailability was observed in the thigh compared with the abdomen. Although  $T_{max}$  and half-life were similar among injection sites,  $C_{max}$  was lower in the thigh than in the abdomen. Based on these data, the differences in bioavailability were not considered clinically relevant, and the three injection sites can be used interchangeably.

In the LEAD-6 trial, a direct comparison between liraglutide 1.8 mg once/day and exenatide 10 µg twice/day demonstrated that steady-state levels of liraglutide were maintained for 24 hours after administration, with a mean  $C_{max}$  and  $C_{min}$  of 17.0 and 6.7 nmol/L, respectively, and a mean AUC of 282.1 nmol•hour/ml.<sup>40</sup> In contrast, exenatide concentrations rapidly peaked and subsequently declined to a nadir 10–12 hours after each injection, with variations observed between morning and afternoon (morning  $C_{max}$  138.2 pmol/L,  $C_{min}$  27.4 pmol/L, and AUC 707.9 pmol•hr/ml; afternoon  $C_{max}$  155.1 pmol/L,  $C_{min}$  35.3 pmol/L, and AUC 1125.8 pmol•hr/ml). The stable liraglutide concentration is most probably due to protraction by albumin binding, with only 1–2% being free at any time. Minimal variations in the mean concentrations can affect the sustained glucose-lowering effect over a 24-hour period.

## Drug Interactions

Liraglutide delays gastric emptying and could affect the absorption pattern of concomitant drugs. The effect of subcutaneous liraglutide 1.8 mg on the pharmacokinetic properties of atorvastatin 40 mg, griseofulvin 500 mg, lisinopril 20 mg, and digoxin 1 mg was evaluated in healthy subjects.<sup>41</sup> The AUCs of griseofulvin and atorvastatin were equivalent among liraglutide-treated and placebo-treated subjects. However, the AUCs of lisinopril and digoxin ( $AUC_{0-72}$ ) were decreased by 15% and 16%, respectively. The  $C_{max}$  for atorvastatin, lisinopril, and digoxin was decreased by 38%, 27%, and 31%, respectively, and the  $C_{max}$  for griseofulvin was increased by 37%. The  $T_{max}$  for atorvastatin, lisinopril, and digoxin was delayed by 1.25, 2.0, and 1.12 hours, respectively, confirming a liraglutide-induced shift in absorption kinetics. In a similar study assessing the effect on the pharmacokinetic exposure of acetaminophen after administration of liraglutide 1.8 mg, a lower acetaminophen  $C_{max}$  and delay in  $T_{max}$  by 15 minutes was observed in the liraglutide group compared with placebo.<sup>42</sup>

In postmenopausal healthy women, the effect of liraglutide 1.8 mg/day on the pharmacokinetics of a low-dose oral contraceptive (ethinylestradiol-levonorgestrel) was investigated.<sup>43</sup> The  $C_{max}$  of ethinylestradiol and levonorgestrel was 12% and 13%, respectively, lower with liraglutide than with placebo, and both compounds reached  $C_{max}$  approximately 1.5 hours later with liraglutide than with placebo. Due to the lack of clinically relevant changes in the overall exposure of ethinylestradiol and levonorgestrel, it is anticipated that their contraceptive effect would remain unaffected when administered with liraglutide.

The effect of liraglutide on the pharmacokinetic properties of other commonly used drugs needs to be further investigated.

## Pharmacodynamics

### Fasting Plasma Glucose Level

The effect of a single, subcutaneous dose of liraglutide 10  $\mu$ g/kg on fasting and prandial concentrations of glucose and glucagon, insulin secretion rate, gastric emptying, and baseline and glucose-induced insulin release was assessed in patients with type 2 diabetes.<sup>35</sup> Liraglutide significantly reduced fasting plasma glucose levels compared with placebo (mean  $\pm$  SD 124.3  $\pm$  18.0 vs 145.9  $\pm$  18.0 mg/dl). In another study, subcutaneous liraglutide 0.6 mg once/day

improved glycemic control, and this effect was significant after the first week and persisted throughout the duration of the study (8 wks).<sup>44</sup> The difference observed in fasting serum glucose level between liraglutide and placebo after 8 weeks was -39.1 mg/dl (95% CI -63.1 to -15.0 mg/dl,  $p=0.002$ ). Similar effects of liraglutide on fasting plasma glucose level have been observed in other clinical studies.<sup>45, 46</sup>

Several studies have demonstrated that liraglutide reduces fasting plasma glucose levels in combination with glimepiride, metformin, or both glimepiride and metformin.<sup>47</sup> Fasting plasma glucose levels decreased within 2 weeks of randomization in the liraglutide and glimepiride groups: mean  $\pm$  SD 164.0  $\pm$  45.0, 153.2  $\pm$  46.8, 153.2  $\pm$  43.2, and 160.4  $\pm$  45.0 mg/dl in the liraglutide 0.6-mg, 1.2-mg, and 1.8-mg groups, and the glimepiride group, respectively. The decrease in fasting plasma glucose level from baseline for all liraglutide groups (-19.8, -28.8, and -30.6 mg/dl for 0.6-, 1.2- and 1.8-mg liraglutide groups, respectively) was significantly greater than the placebo group (-7.2 mg/dl), but similar to the decrease observed in the glimepiride group (-23.4 mg/dl).

Results from the LEAD-6 study demonstrated that liraglutide 1.8 mg once/day reduced mean fasting plasma glucose levels more than exenatide 10  $\mu$ g twice/day in patients with inadequately controlled type 2 diabetes (-29.0 vs -10.8 mg/dl).<sup>48</sup>

### Postprandial Glucose and Hemoglobin A<sub>1c</sub> Levels

Liraglutide significantly lowers postprandial glucose levels in healthy subjects.<sup>8, 35</sup> In patients with type 2 diabetes, treatment with liraglutide 0.6 mg once/day showed a significant decrease in A1C levels compared with placebo (-0.80%, 95% CI -1.50% to -0.09%,  $p=0.028$ ).<sup>44</sup> The AUC for serum glucose was significantly suppressed in the liraglutide group compared with placebo after 3 days. Similarly, a significant reduction by approximately 20% in 24-hour glucose AUC and postprandial glucose level after liraglutide injection was observed in another study in patients with type 2 diabetes.<sup>34</sup>

In a 14-week study investigating the efficacy of liraglutide monotherapy, the A1C level was dose-dependently reduced from baseline (~8.3%) compared with an increase of 0.29% for placebo, with 46% of patients reaching the A1C goal of less than 7% compared with 5% for placebo.<sup>46</sup> The LEAD-6 study was the first

comparison of liraglutide versus exenatide in subjects who had not achieved adequate glycemic control despite treatment with metformin and/or sulfonylureas.<sup>48</sup> Significantly more subjects achieved A1C levels of less than 7% with liraglutide than with exenatide (54% vs 43%). In keeping with these data, 35% of liraglutide-treated patients achieved A1C levels of 6.5% or lower compared with 21% for exenatide. Postprandial glucose level was reduced more with exenatide than with liraglutide after breakfast and dinner, but not after lunch or at bedtime.

It was demonstrated in the LEAD-2 study that mean postprandial glucose levels from self-monitored 7-point plasma glucose measurements decreased from baseline in response to liraglutide 0.6–1.8 mg once/day.<sup>47</sup> The decreases in the 1.2- and 1.8-mg liraglutide groups were comparable to those in the glimepiride group (–41.4 and –46.9 mg/dl for liraglutide 1.2 mg and 1.8 mg, respectively, and –45.1 mg/dl for glimepiride). Within 12 weeks of the study, mean A1C levels for the overall population decreased from baseline in all liraglutide groups and in the glimepiride group, whereas a slight increase was observed in the placebo group. Liraglutide-treated subjects had superior glycemic control compared with those in the placebo group (0.6 mg –0.8% [95% CI –1.0% to –0.6%]; 1.2 mg –1.1% [–1.3% to –0.9%]; and 1.8 mg –1.1% [–1.3% to –0.9%]). Treatment differences in A1C levels between liraglutide and glimepiride demonstrated that liraglutide doses of 1.2 and 1.8 mg were noninferior to treatment with glimepiride (liraglutide 1.2 mg vs glimepiride 0.0% [95% CI –0.2% to 0.2%] and liraglutide 1.8 mg vs glimepiride 0.0% [95% CI –0.2% to 0.2%]).

In Japanese patients with type 2 diabetes, liraglutide dose-dependently reduced A1C levels by 0.79–1.85% relative to placebo by week 14, with 75% and 57% of patients reaching A1C target levels of less than 7% and 6.5%, respectively.<sup>49</sup> The LEAD-3 trial demonstrated that A1C levels decreased from baseline by 0.84% with liraglutide 1.2 mg, 1.14% with liraglutide 1.8 mg, and 0.51% with glimepiride.<sup>50</sup> The percentage decreases in A1C in the liraglutide treatment groups were significantly greater than those in the glimepiride group. Postprandial glucose concentrations from self-monitored 8-point plasma glucose profiles decreased in all three treatment groups.

Taken together, data from several clinical studies demonstrate that through its effects on

both fasting and postprandial glucose levels, liraglutide improves and maintains glycemic control.

### $\beta$ -Cell Function in Type 2 Diabetes

In type 2 diabetes, loss of  $\beta$ -cell function may be mediated by high concentrations of free fatty acids such as palmitate and oleate, which have been shown to induce  $\beta$ -cell apoptosis in vitro.<sup>51–53</sup> Glucagon-like peptide-1 has direct effects on pancreatic  $\beta$ -cells, inducing glucose-dependent insulin secretion, insulin biosynthesis, and GLUT-2 (the  $\beta$ -cell glucose transporter) and glucokinase expression, in addition to enhancing  $\beta$ -cell proliferation and differentiation.<sup>54, 55</sup> Although its effects on  $\beta$ -cell mass have not yet been clearly demonstrated in clinical studies, the beneficial effects of liraglutide on islet cells have been routinely seen. It has also been demonstrated that insulin secretory capacity, as measured by homeostasis model assessment (HOMA) was increased by approximately 50% after liraglutide treatment, whereas insulin sensitivity remained unchanged.<sup>35</sup>

A single dose of liraglutide significantly increased insulin and C-peptide levels and substantially improved the overall insulin secretory response, thus restoring  $\beta$ -cell sensitivity to glucose in adults with type 2 diabetes.<sup>56</sup> The effects of liraglutide in enhancing the insulin secretory response became evident after 40–60 minutes of glucose infusion when plasma glucose levels reached 108–126 mg/dl. The glucose dependency of the effect of liraglutide on insulin secretion has been well demonstrated in normal patients and in patients with type 2 diabetes.<sup>57, 58</sup> A lack of effect of liraglutide on insulin secretion in euglycemic conditions indicates that this drug might not lead to inappropriate insulin secretion, in turn limiting the risk of hypoglycemia.

Treatment with liraglutide for 1 week improved glucose-induced insulin secretion and  $\beta$ -cell function (HOMA-B, insulin secretion during a hyperglycemic clamp, maximal insulin secretion after arginine infusion, and proinsulin:insulin ratio), and had significant effects on  $\alpha$ -cell function.<sup>34</sup> After 7 days of daily liraglutide subcutaneous injections, short-term  $\beta$ -cell function significantly improved under conditions of normal living with an upward shift and steeper  $\beta$ -cell dose-response curve, which was associated with improvements in glucose levels.<sup>59</sup> Liraglutide has been associated with improved  $\beta$ -cell function, which was similar to that observed

with glimepiride<sup>47, 50, 60</sup> and superior to rosiglitazone<sup>61</sup> or exenatide.<sup>48</sup>

Animal studies have indicated that liraglutide can increase  $\beta$ -cell mass and inhibit apoptosis in a dose-dependent manner.<sup>5, 62, 63</sup> In rodents, GLP-1 analogs have been shown to induce increased  $\beta$ -cell mass both in vitro and in vivo.<sup>64, 65</sup> Using primary neonatal rat islet cells, liraglutide was demonstrated to be a potent inhibitor of both cytokine-, free fatty acid-, and streptozotocin-mediated apoptosis in  $\beta$  cells.<sup>62</sup>  $\beta$ -Cell replication was found to be increased,<sup>66</sup> and similar effects in cultured human islet cells were recently reported.<sup>5</sup> These effects of liraglutide may facilitate preservation of  $\beta$ -cell mass in patients with type 2 diabetes.

### Weight Loss

In some studies, weight loss with liraglutide has been inconsistent. In earlier studies, no clear dose response was observed between liraglutide and weight loss.<sup>44, 45, 67</sup> With higher doses (up to 1.9 mg/day), weight reductions have generally been seen consistently. However in the LEAD-1 study, the weight change was not significantly different from placebo.<sup>61</sup> Nausea, a common gastrointestinal adverse event, may contribute to the weight loss observed with GLP-1 analogs.

In the LEAD-3 study, participants in the liraglutide 1.2- and 1.8-mg groups lost weight, in contrast to subjects taking glimepiride, who gained weight.<sup>50, 60</sup> Weight loss in the first 16 weeks was sustained throughout the 52-week study. To determine if nausea played a role in weight loss, participants were analyzed by the number of days that nausea was present ( $> 7$  or  $\leq 7$  days). No significant differences were observed for any treatment group ( $-3.24$  kg,  $-3.39$  kg, and  $-1.43$  kg, respectively, for liraglutide 1.2 mg, liraglutide 1.8 mg, and glimepiride 8.0 mg in the  $> 7$ -day group, and  $-1.85$  kg,  $-2.26$  kg, and  $1.22$  kg, respectively, in the  $\leq 7$ -day group). These data argue against nausea and vomiting being the mechanism behind the weight loss observed with liraglutide treatment.

Another possible cause of weight loss is decreased food intake. Studies using visual analog scales have demonstrated that liraglutide reduced the feelings of hunger and food intake, while increasing the feeling of fullness, together leading to a lower energy intake by up to 18% during an ad libitum meal.<sup>68</sup> To support the hypothesis that a decrease in food intake could

possibly underlie the liraglutide-mediated effect on weight loss, several animal studies have documented the effect of liraglutide on food intake. The effect of food intake and body weight of twice-daily subcutaneous liraglutide for 10 days was examined.<sup>69</sup> Acute intravenous administration of high doses of GLP-1 (100 and 500  $\mu$ g/animal) decreased food intake at 30 and 60 minutes after dosing. Peripheral administration of liraglutide significantly inhibited nighttime food intake in rats.<sup>70</sup> In addition, liraglutide conferred lasting and reversible anorexia with accompanying weight loss and reduction of body adiposity in rats. In summary, it appears that the mechanism underlying decreased food intake most likely consists of a combination of inhibition of gastric emptying, in turn leading to a sensation of fullness, and the binding of liraglutide to GLP-1 receptors in the area postrema of the brain stem.

### Gastric Emptying

A single dose of liraglutide significantly delayed gastric emptying.<sup>33</sup> Gastric emptying in healthy volunteers was significantly delayed as measured by the AUC of 3-*O*-methylglucose during the prandial period. The 3-*O*-methylglucose peak was 15 minutes retarded after a single injection of liraglutide. However, in patients with type 2 diabetes, liraglutide failed to have an effect on gastric emptying as assessed by acetaminophen levels following ingestion.<sup>34</sup> Subsequently it has been shown that liraglutide, at doses up to 1.8 mg/day, is associated with a minor delay in gastric emptying, particularly over the first hour.<sup>68</sup> Liraglutide acts on GLP-1 receptors in the brain to delay the absorption of food by decreasing gastric emptying and acid secretion.<sup>28</sup>

### Energy Expenditure

An assessment of body composition showed that liraglutide was associated with a small trend toward a reduction in total fat mass and an increase in lean body mass.<sup>44</sup> However, liraglutide did not affect 24-hour resting energy expenditure, at least in doses up to 0.6 mg/day. On the contrary, at doses up to 1.8 mg/day, there was only a nonsignificant trend for higher resting energy expenditure.<sup>68</sup>

### Effects on Glucagon Level

Reports on the effect of liraglutide on glucagon

levels have been controversial. In healthy volunteers, after a single dose of liraglutide, postprandial glucagon levels were significantly suppressed.<sup>35</sup> When given as monotherapy, liraglutide significantly lowered fasting glucagon concentration, specifically in the 1.9-mg liraglutide group compared with placebo.<sup>46</sup>

Patients with type 2 diabetes treated with liraglutide had comparable fasting glucagon levels to those of patients receiving placebo, but had a significantly reduced glucagon level response to meal-related hyperglycemia and after an arginine stimulation test.<sup>34</sup> In contrast, another study showed no significant difference in glucagon levels between those receiving liraglutide and placebo.<sup>31</sup> Similarly, glucagon levels in patients with diabetes treated with liraglutide or placebo were only marginally different.<sup>56</sup> Another study also failed to show a significant difference in glucagon levels in patients receiving liraglutide or placebo.<sup>45</sup>

#### Cardiovascular Effects

Modest increases in pulse rate (~2–3 beats/min) have been observed throughout the LEAD studies.<sup>47, 50, 60, 71</sup> Of interest, there have been several consistent reports that systolic blood pressure was significantly decreased. One study found reductions with all liraglutide doses, up to 7.9 mm Hg compared with placebo after 14 weeks of treatment.<sup>46</sup> In the LEAD-2 and LEAD-3 studies, systolic blood pressure changes favored liraglutide over glimepiride, characterized by reductions from baseline of 2–4 mm Hg with liraglutide.<sup>47, 50, 60</sup> The 1.2- and 1.8-mg liraglutide groups had significant reductions in systolic blood pressure of 2–3 mm Hg compared with an increase of 0.4 mm Hg in the glimepiride group. Reductions in systolic blood pressure were also noted as early as 2 weeks after randomization in the other LEAD studies.<sup>72</sup> The mechanisms associated with the increased pulse rate and decreased systolic blood pressure noted in the LEAD studies are not known. Changes in diastolic pressure have not been reported in any clinical studies so far.

Cardioprotective effects of GLP-1 have been observed in animal studies. In a rat ischemia-reperfusion model, GLP-1 added before ischemia demonstrated a significant reduction in myocardial infarction.<sup>73</sup> Clinically, it is speculated that reductions in systolic blood pressure could be associated with weight loss. To support the cardioprotective effect, it has been

demonstrated that the weight loss induced by liraglutide is due to a loss of visceral fat (and not lean tissue), which is a known cardiovascular risk factor.<sup>74</sup> However, reductions in blood pressure are also observed with DPP-4 inhibitors, which are weight neutral.<sup>75, 76</sup> Additional data from ongoing clinical trials may help elucidate the mechanisms underlying liraglutide-induced changes in pulse and blood pressure. Patients with type 2 diabetes and hypertension may receive additional vascular benefits by using a new drug therapy that improves glycemic control and also lowers systolic blood pressure.

#### Conclusion

Currently, there exists an unmet medical need in the diabetes therapeutic area to enable maintenance of long-term glycemic control. Liraglutide is a new treatment for patients with type 2 diabetes that addresses pathologic aspects of the disease that are not addressed by traditional therapeutic regimens. The pharmacokinetic profile of liraglutide is dose linear, is predictable, demonstrates minimal variability, and supports once-daily dosing. Clinical studies have clearly demonstrated that liraglutide, with its enhanced plasma half-life, provides 24-hour coverage to improve glycemic control through effects on both fasting and postprandial glucose levels. Furthermore, in preclinical and clinical studies, liraglutide has been consistently shown to improve  $\beta$ -cell function, leading to increased insulin sensitivity. In addition to improving glycemic control, desirable effects of liraglutide include weight loss and a decrease in systolic blood pressure, which may encourage patients and clinicians to use this drug, especially for patients with type 2 diabetes and hypertension. The effects of liraglutide on long-term microvascular and macrovascular complications, however, often resulting from inadequate glycemic control, are yet to be determined.

#### Acknowledgment

The author wishes to thank Anu Santhanagopal, Ph.D., of DesignWrite, LLC, for providing writing and editorial assistance.

#### References

1. International Diabetes Federation. Diabetes atlas, 3rd ed. Brussels, Belgium: International Diabetes Federation, 2007. Available from <http://www.eatlas.idf.org>.
2. Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on

- diabetes in the United States. Atlanta, GA: U.S. Department of Health and Human Services, 2007.
3. **National Institutes of Health.** National diabetes statistics 2007—prevalence of diagnosed and undiagnosed diabetes in the United States, all ages, 2007. Available from <http://diabetes.niddk.nih.gov/dm/pubs/statistics/#allages>. Accessed August 14, 2009.
  4. **Weir GC, Bonner-Weir S.** Five stages of evolving  $\beta$ -cell dysfunction during progression to diabetes. *Diabetes* 2004;53(suppl 3):S16–21.
  5. **Wajchenberg BL.** Beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 2007;28:187–218.
  6. **United Kingdom Prospective Diabetes Study Group.** Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249–58.
  7. **Kieffer TJ, Habener JF.** The glucagon-like peptides. *Endocr Rev* 1999;20:876–913.
  8. **Agero H, Vicini P.** Pharmacodynamics of NN2211, a novel long acting GLP-1 derivative. *Eur J Pharm Sci* 2003;19:141–50.
  9. **Holst JJ, Orskov C, Nielsen OV, Schwartz TW.** Truncated glucagon-like peptide I, an insulin-releasing hormone from the distal gut. *FEBS Lett* 1987;211:169–74.
  10. **Kreymann B, Williams G, Ghatel MA, Bloom SR.** Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet* 1987;2:1300–4.
  11. **Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ.** Truncated GLP-1 (proglucagon 78–107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 1993;38:665–73.
  12. **Naslund E, Barkeling B, King N, et al.** Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. *Int J Obes Relat Metab Disord* 1999;23:304–11.
  13. **Naslund E, Bogefors J, Skogar S, et al.** GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol Regul Integr Comp Physiol* 1999;277:R910–16.
  14. **Edvell A, Lindstrom P.** Initiation of increased pancreatic islet growth in young normoglycemic mice (Umea +/-). *Endocrinology* 1999;140:778–83.
  15. **Willms B, Werner J, Holst JJ, Orskov C, Creutzfeldt W, Nauck MA.** Gastric emptying, glucose responses, and insulin secretion after a liquid test meal: effects of exogenous glucagon-like peptide-1 (GLP-1)-(7-36) amide in type 2 (noninsulin-dependent) diabetic patients. *J Clin Endocrinol Metab* 1996;81:327–32.
  16. **Rachman J, Barrow BA, Levy JC, Turner RC.** Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia* 1997;40:205–11.
  17. **Meier JJ, Nauck MA, Kranz D, et al.** Secretion, degradation, and elimination of glucagon-like peptide 1 and gastric inhibitory polypeptide in patients with chronic renal insufficiency and healthy control subjects. *Diabetes* 2004;53:654–62.
  18. **Kieffer TJ, McIntosh CHS, Pederson RA.** Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide I in vitro and in vivo by dipeptidyl peptidase IV. *Endocrinology* 1995;136:3585–96.
  19. **Mentlein R, Gallwitz B, Schmidt WE.** Dipeptidyl-peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1(7-36)amide, peptide histidine methionine and is responsible for their degradation in human serum. *Eur J Biochem* 1993;214:829–35.
  20. **Gutniak MK, Linde B, Holst JJ, Efendic S.** Subcutaneous injection of the incretin hormone glucagon-like peptide 1 abolishes postprandial glycemia in NIDDM. *Diabetes Care* 1994;17:1039–44.
  21. **Knudsen LB, Nielsen PF, Huusfeldt PO, et al.** Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 2000;43:1664–9.
  22. **Pridal L, Deacon CF, Kirk O, Christensen JV, Carr RD, Holst JJ.** Glucagon-like peptide-1(7-37) has a larger volume of distribution than glucagon-like peptide-1(7-36)amide in dogs and is degraded more quickly in vitro by dog plasma. *Eur J Drug Metab Pharmacokinet* 1996;21:51–9.
  23. **Larsen J, Hylleberg B, Ng K, Damsbo P.** Glucagon-like peptide-1 infusion must be maintained for 24 h/day to obtain acceptable glycemia in type 2 diabetic patients who are poorly controlled on sulphonylurea treatment. *Diabetes Care* 2001;24:1416–21.
  24. **Quddusi S, Vahl TP, Hanson K, Prigeon RL, D'Alessio DA.** Differential effects of acute and extended infusions of glucagon-like peptide-1 on first- and second-phase insulin secretion in diabetic and nondiabetic humans. *Diabetes Care* 2003;26:791–8.
  25. **Holst JJ.** The physiology and pharmacology of incretins in type 2 diabetes mellitus. *Diabetes Obes Metab* 2008;10:14–21.
  26. **Deacon CF.** Potential of liraglutide in the treatment of patients with type 2 diabetes. *Vasc Health Risk Manag* 2009;5:199–211.
  27. **Agero H, Jensen LB, Elbrond B, Rolan P, Zdravkovic M.** The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* 2002;45:195–202.
  28. **Steengaard DB, Thomsen JK, Olsen HB, Knudsen LB.** The molecular basis for the delayed absorption of the once-daily human GLP-1 analogue, liraglutide [abstract]. *Diabetes* 2008;57:A164.
  29. **Deacon CF, Knudsen LB, Madsen K, Wiberg FC, Jacobsen O, Holst JJ.** Dipeptidyl peptidase IV resistant analogues of glucagon-like peptide-1 which have extended metabolic stability and improved biological activity. *Diabetologia* 1998;41:271–8.
  30. **Bjornsdottir I, Olsen A, Larsen U, et al.** Metabolism and excretion of the once-daily human GLP-1 analogue liraglutide in healthy subject and its in vitro degradation by dipeptidyl peptidase IV and neutral endopeptidase [abstract]. *Diabetologia* 2008;51:S356.
  31. **Elbrond B, Jakobsen G, Larsen S, et al.** Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. *Diabetes Care* 2002;25:1398–404.
  32. **Irie S, Matsumura Y, Zdravkovic M, Jacobsen LV, Kageyama S.** Tolerability, pharmacokinetics and pharmacodynamics of the once-daily human GLP-1 analog liraglutide in Japanese healthy subjects: a randomized, double-blind, placebo-controlled dose-escalation study. *Int J Clin Pharmacol Ther* 2008;46:273–9.
  33. **Damholt B, Golor G, Wierich W, Pedersen P, Eklom M, Zdravkovic M.** An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. *J Clin Pharmacol* 2006;46:635–41.
  34. **Degn KB, Juhl CB, Sturis J, et al.** One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and  $\alpha$ - and  $\beta$ -cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 2004;53:1187–94.
  35. **Juhl CB, Hollingdal M, Sturis J, et al.** Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in type 2 diabetes. *Diabetes* 2002;51:424–9.
  36. **Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M.** Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide [published online ahead of print September 1, 2009]. *Br J Clin Pharmacol*. Available from <http://dx.doi.org/10.1111/j.1365-2125.2009.03536.x>.
  37. **Davidson JA, Falahati A, Brett J.** Mild renal impairment has no effect on the efficacy and safety of liraglutide. Presented at the 18th annual meeting and clinical congress of the American Association of Clinical Endocrinologists, Houston, TX, May 13–17, 2009.
  38. **Flint A, Nazzal K, Jagielski P, Segel S, Zdravkovic M.** Influence of hepatic impairment on pharmacokinetics of the long-acting human GLP-1 analogue liraglutide [abstract]. *Diabetes* 2007;56:A145.
  39. **Kapitzka C, Flint A, Spitzer H, Hindsberger C, Zdravkovic M.**

- The effect of three different injection sites on the pharmacokinetics of the once-daily human GLP-1 analogue liraglutide [abstract]. *Diabetes* 2008;57:A593.
40. Rosenstock J, Gumprecht J, Szyprowska E, et al. Pharmacokinetics of liraglutide vs exenatide in type 2 diabetes: sustained vs fluctuating concentrations over 24 hours [abstract]. *Diabetes* 2009;58:A150.
  41. Malm-Erfjelt M, Ekblom M, Brondsted L, Vouis J, Lennernas H, Zdravkovic M. A randomised, double-blind, cross-over trial investigating the effect of liraglutide on the absorption pharmacokinetics of concomitantly administered oral drugs in healthy subjects [abstract]. *Diabetes* 2008;57:A130.
  42. Kapitza C, Flint A, Hindsberger C, Zdravkovic M. The effect of the once-daily human GLP-1 analogue liraglutide on the pharmacokinetics of paracetamol [abstract]. *Diabetes* 2008;57:A593.
  43. Jacobsen LV, Brondsted L, Vouis J, Zdravkovic M. A randomized, double-blind, cross-over trial investigating the effect of liraglutide on the absorption of an oral contraceptive drug [abstract]. *Diabetes* 2008;57:A566.
  44. Harder H, Nielsen L, Thi TD, Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care* 2004;27:1915–21.
  45. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 2004;27:1335–42.
  46. Vilsholt T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human GLP-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes mellitus. *Diabetes Care* 2007;30:1608–10.
  47. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009;32:84–90.
  48. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009;374:39–47.
  49. Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: a double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes. *Diabetes Res Clin Pract* 2008;81:161–81.
  50. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2008;373:473–81.
  51. Shimabukuro M, Zhou YT, Levi M, Unger RH. Fatty acid-induced  $\beta$  cell apoptosis: a link between obesity and diabetes. *Proc Natl Acad Sci U S A* 1998;95:2498–502.
  52. Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, Donath MY. Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. *Diabetes* 2001;50:69–76.
  53. Unger RH, Orci L. Diseases of liporegulation: new perspective on obesity and related disorders. *FASEB J* 2001;15:312–21.
  54. Perfetti R, Merkel P. Glucagon-like peptide-1: a major regulator of pancreatic beta-cell function. *Eur J Endocrinol* 2000;143:717–25.
  55. Nielsen JH, Galsgaard ED, Moldrup A, et al. Regulation of beta-cell mass by hormones and growth factors. *Diabetes* 2001;50(suppl 1):S25–9.
  56. Chang AM, Jakobsen G, Sturis J, et al. The GLP-1 derivative NN2211 restores  $\beta$ -cell sensitivity to glucose in type 2 diabetic patients after a single dose. *Diabetes* 2003;52:1786–91.
  57. Abraham EJ, Leech CA, Lin JC, Zulewski H, Habener JF. Insulinotropic hormone glucagon-like peptide-1 differentiation of human pancreatic islet-derived progenitor cells into insulin-producing cells. *Endocrinology* 2002;143:3152–61.
  58. Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1993;36:741–4.
  59. Mari A, Degn K, Brock B, Rungby J, Ferrannini E, Schmitz O. Effects of the long-acting human GLP-1 analogue liraglutide on beta-cell function in normal living conditions. *Diabetes Care* 2007;30:2032–3.
  60. Garber A, Henry R, Ratner R, et al. Significantly better glycemic control and weight reduction with liraglutide, a once-daily human GLP-1 analog, compared with glimepiride: all as monotherapy in type 2 diabetes [abstract]. *Diabetes* 2008;57:LB3.
  61. Marre M, Shaw J, Brandle M, et al. Liraglutide, a once-daily human GLP-1 analog, added to sulfonylurea (SU) offers significantly better glycemic control and favorable weight change compared with rosiglitazone and SU combination therapy in subjects with type 2 diabetes [abstract]. *Diabetes* 2008;57:A4.
  62. Bregenholt S, Moldrup A, Blume N, et al. The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits  $\beta$ -cell apoptosis in vitro. *Biochem Biophys Res Commun* 2005;330:577–84.
  63. Sturis J, Gotfredsen CF, Romer J, et al. GLP-1 derivative liraglutide in rats with beta-cell deficiencies: influence of metabolic state on beta-cell mass dynamics. *Br J Pharmacol* 2003;140:123–32.
  64. Perfetti R, Zhou J, Doyle ME, Egan JM. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. *Endocrinology* 2000;141:4600–5.
  65. Buteau J, Roduit R, Susini S, Prentki M. Glucagon-like peptide-1 promotes DNA synthesis, activates phosphatidylinositol 3-kinase and increases transcription factor pancreatic and duodenal homeobox gene 1 (PDX-1) DNA binding activity in beta (INS-1)-cells. *Diabetologia* 1999;42:856–64.
  66. Friedrichsen BN, Neubauer N, Lee YC, et al. Stimulation of pancreatic beta-cell replication by incretins involves transcriptional induction of cyclin D1 via multiple signalling pathways. *J Endocrinol* 2006;188:481–92.
  67. Feinglos MN, Saad MF, Pi-Sunyer FX, An B, Santiago O. Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with type 2 diabetes [abstract]. *Diabet Med* 2005;22:1023.
  68. Horowitz M, Flint A, Doran S, et al. Effects of the once-daily human GLP-1 analogue liraglutide on appetite and energy intake in type 2 diabetes [abstract]. *Diabetologia* 2008;51:S355.
  69. Larsen PJ, Fledelius C, Knudsen LB, Tang-Christensen M. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. *Diabetes* 2001;50:2530–9.
  70. Raun K, von Voss P, Knudsen LB. Liraglutide, a once-daily human glucagon-like peptide-1 analog, minimizes food intake in severely obese minipigs. *Obesity (Silver Spring)* 2007;15:1710–16.
  71. Zinman B, Gerich J, Buse J, et al. Effect of the GLP-1 analog liraglutide on glycemic control and weight reduction in patients on metformin and rosiglitazone: a randomized double-blind placebo-controlled trial [abstract]. *Diabetologia* 2008;51:S359.
  72. Colagiuri S, Frid A, Zdravkovic M, et al. Liraglutide, a human GLP-1 analogue, reduces systolic blood pressure in subjects with type 2 diabetes [abstract]. *Diabetologia* 2008;51:S360.
  73. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 2005;54:146–51.
  74. Jendle J, Nauck MA, Matthews D, et al. Liraglutide, a once-daily human GLP-1 analog, reduces fat percentage, visceral and

subcutaneous adipose tissue and hepatic steatosis compared with glimepiride when added to metformin in subjects with type 2 diabetes [abstract]. *Diabetes* 2008;57:A32-3.

75. Mistry GC, Maes AL, Lasseter KC, et al. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. *J Clin Pharmacol* 2008;48:592-8.
76. Bosi E, Byiers SR, Cohen SE. Vildagliptin significantly decreases blood pressure (BP) in hypertensive patients (pts) with type 2 diabetes (T2DM) compared with metformin [abstract]. *Diabetes* 2007;56:A139.