

Pharmacokinetics and Pharmacodynamics of a New Rapid Acting Insulin Formulation Vialog™ In The Diabetic Swine Model

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Abstract

The aim of this study was to evaluate the pharmacodynamic (PD) and pharmacokinetic (PK) properties of "Vialog™", a novel insulin formulation. Vialog™ is a formulation of insulin lispro and excipients used with Viaject® that increases the rate of subcutaneous absorption. Eight miniature diabetic swine were given a dose of 0.25 U/kg insulin lispro (IL) or the new enhanced formulation Vialog™ containing insulin lispro (ILV). Immediately following dosing the swine were fed 500 g of their normal swine diet. Blood glucose and plasma insulin were sampled at -30, -20, -10, 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 240, 300, 360, 420, and 480 min. post dose. Insulin lispro was measured by ELISA method, and plasma glucose was determined using a YSI glucose measurement (mg/dL). Results of timing-related PK and PD parameters are shown in Table 1. The results confirm ILV had significantly faster absorption than IL and faster elimination. The PD is consistent with the PK. In conclusion, a more rapid onset of action and insulin profile may be obtained by enhancing the typical insulin lispro formulation with safe excipients designed to enhance the absorption of insulin from the site of injection.

Introduction

One of the key improvements in insulin treatments was the introduction in the 1990s of rapid-acting insulin analogs, such as Humalog®, NovoLog® and Apidra®. However, even with the rapid-acting insulin analogs, peak insulin levels typically occur within 50 to 70 minutes following the injection. Because the rapid-acting insulin analogs do not adequately mimic the first-phase insulin release, diabetics using insulin therapy continue to have inadequate levels of insulin present at the initiation of a meal and too much insulin present between meals. This lag in insulin delivery can result in hyperglycemia early after meal onset. Furthermore, the excessive insulin between meals may result in an abnormally low level of blood glucose known as hypoglycemia. Hypoglycemia can result in loss of mental acuity, confusion, increased heart rate, hunger, sweating and faintness. At very low glucose levels, hypoglycemia can result in loss of consciousness, coma and even death. According to the American Diabetes Association, or ADA, insulin-using diabetic patients have on average 1.2 serious hypoglycemic events per year, many of which require hospital emergency room visits by the patients.

Because the time-course of insulin delivery to the blood plays such an important role in overall glucose control, there is significant need for an injectable insulin that reaches the blood even more rapidly than the rapid-acting insulin analogs.

The aim of the Viaject® formulation was to make an ultra-rapid formulation using recombinant human insulin that would be a viable alternative to prandial insulin analogs. Viaject® is formulated with a chelating agent and an acid which helps to reduce the charge of the insulin molecule. Its mechanism of rapid action involves rapid dissociation of insulin hexamers post injection, creating a smaller charge masked insulin monomer. It is the monomeric form of insulin that is rapidly absorbed from the subcutaneous injection site, resulting in the lowering of blood glucose.

Clinically, the ultra-rapid onset of action of Viaject® has been demonstrated in a 10-subject, phase I clinical trial with a TGI_{IR}Max50% early of 33±17 min compared to regular human insulin (Humulin R®, 66±15 min) and 51±13 min with insulin lispro (Humalog®) ¹. In addition, in a second study in patients including a standardized meal, Viaject® was significantly more rapid than insulin lispro².

Therefore, it is the object of this study to see if a rapid-acting insulin analog, such as insulin lispro, could also benefit from this technology.

Materials and Methods

Formulations

- Vialog™ was prepared with Humalog® U-100 supplemented with disodium EDTA and citric acid. Comparator was insulin lispro (Lilly Humalog®).

Preclinical Protocol:

- Yucatan™ Miniature Swine (~3 mos. old) were permanently catheterized and allowed to heal. Diabetes was induced using intravenously administered Alloxan at a dose of 100-150 mg/kg. Swine were stabilized at least two weeks prior to use.
- Eight swine were given Vialog™ on the same study day at a dose of 0.25 U/kg. On another study day, insulin lispro was administered to the same eight swine at the same dose. Immediately post injection, the swine were fed 500 g of their normal swine diet. Blood samples were taken over the following 8 hours, at -30, -20, -10, 0, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300, 360, 420 and 480 min. post dose. EDTA plasma samples were immediately processed and stored frozen until shipment under dry ice to Biodel for ELISA insulin and YSI glucose analysis.

Analytical Methods:

- Frozen samples were thawed prior to analysis, mixed and aliquoted for ELISA insulin analysis and YSI glucose testing on the first defrost cycle.
- Plasma glucose analysis:** Plasma glucose levels were determined using a YSI glucose analyzer (YSI Life Sciences).
- Plasma insulin analog analysis:** Mercodia Iso-Insulin ELISA Cat #: 10-1128-01. Method provided with kit and used accordingly. Reported cross-reactivity with insulin lispro is 89%.

Pharmacokinetic and Pharmacodynamic Estimations:

- Pharmacokinetics:** The baseline of each set of raw plasma insulin data was estimated from an average of the pre-dose insulin concentrations. C_{max} and T_{max} identified without non-linear curve fitting for each individual swine. The early and late ½T_{max} was estimated by identifying the time of ½ C_{max} for each swine on the positive (absorption) and negative (elimination) slope of the concentration time curve. Each parameter estimate was tested using a Student's t-test for significance.
- Pharmacodynamics:** The baseline of each set of glucose data was estimated from the average of the pre-dose glucose values. The estimated time to nadir was determined by the lowest glucose value. In addition, to estimate the rapidity of insulin response, the first time at least a 20 point drop from the average baseline level was estimated, as well as the time to ½ nadir. The estimate of "½ nadir" was determined using a linear equation between the time periods that contained the glucose level corresponding to the half way drop to the lowest glucose level. Student's t-tests were used to compare parameter estimates for significance.

Results

- The pharmacokinetic profile of Vialog™ and insulin lispro is shown in Figures 1A and 1B. Figure 1A has the entire 8-hour experiment, while 1B is the first 100 min. A significantly faster absorption (½ T_{max} early) and elimination profile (-½ T_{max} late) was seen with the addition of the excipients EDTA and citric acid compared to insulin lispro alone (Table 1). Vialog™ was more than twice as fast to achieve ½ C_{max} and was eliminated nearly 30% faster than commercially prepared insulin lispro.
- The second set of figures show the percent of glucose baseline vs. time for Vialog™ and insulin lispro for the full 8-hour experiment (Figure 2A) and the first 100 minutes (Figure 2B). The increased absorption of insulin is visualized graphically by the faster glucose response and time back to baseline of the Vialog™ formulation compared to insulin lispro. The same trends are described in Table 1 by a 38% decrease in time to ½ glucose nadir and 60% faster mean time to glucose nadir.

Conclusions

- Vialog™ produced a more rapid absorption profile than insulin lispro. This improvement in the rate of absorption provides a more physiological PK/PD profile, enhancing insulin's signaling properties. In addition, insulin can be more accurately timed with the meal. This precisely timed insulin absorption is useful for both the initial food response and the elimination of the excess insulin after the meal, reducing the chance of postprandial hypoglycemia.

Figure 1A

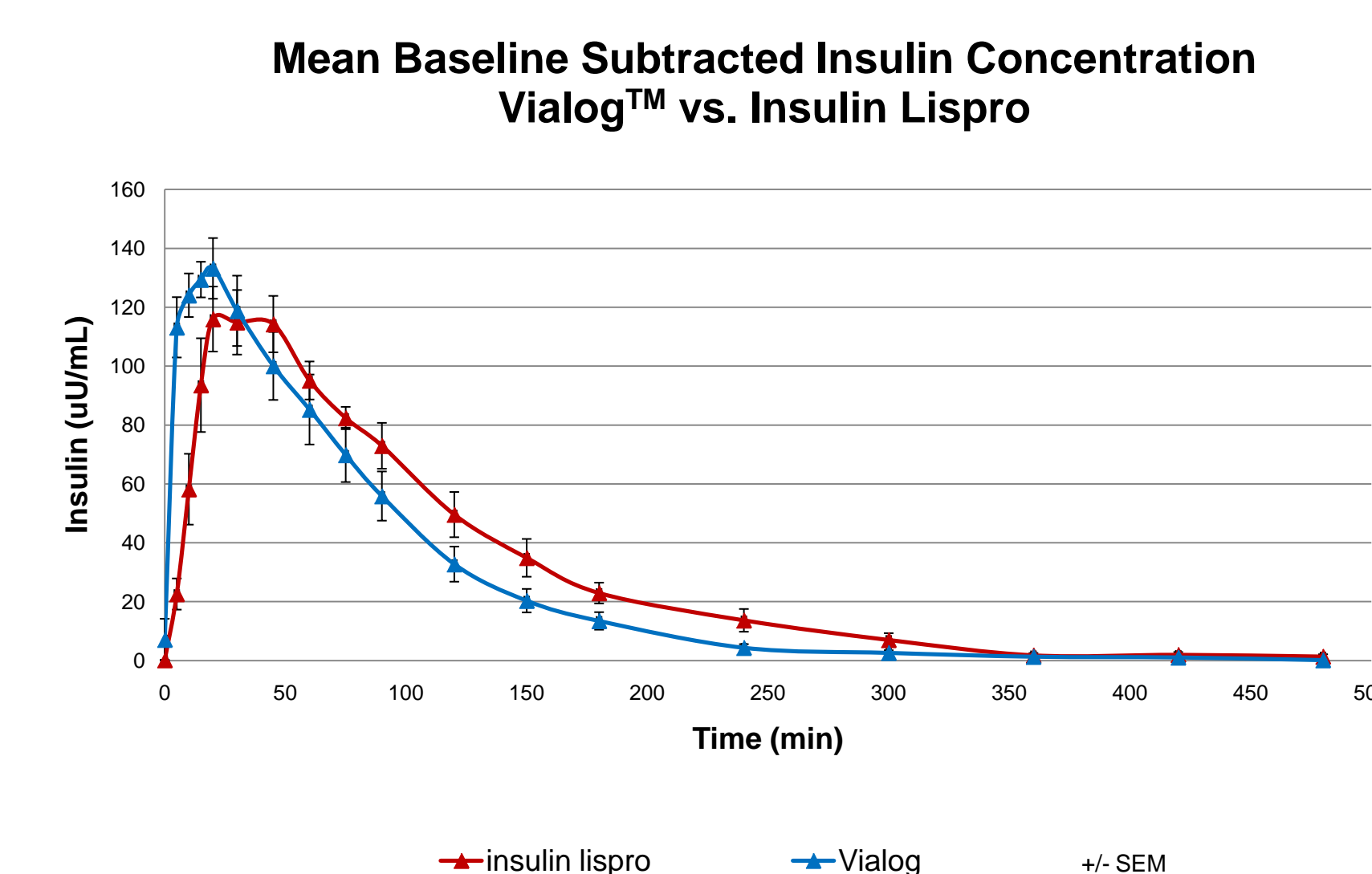


Figure 1B

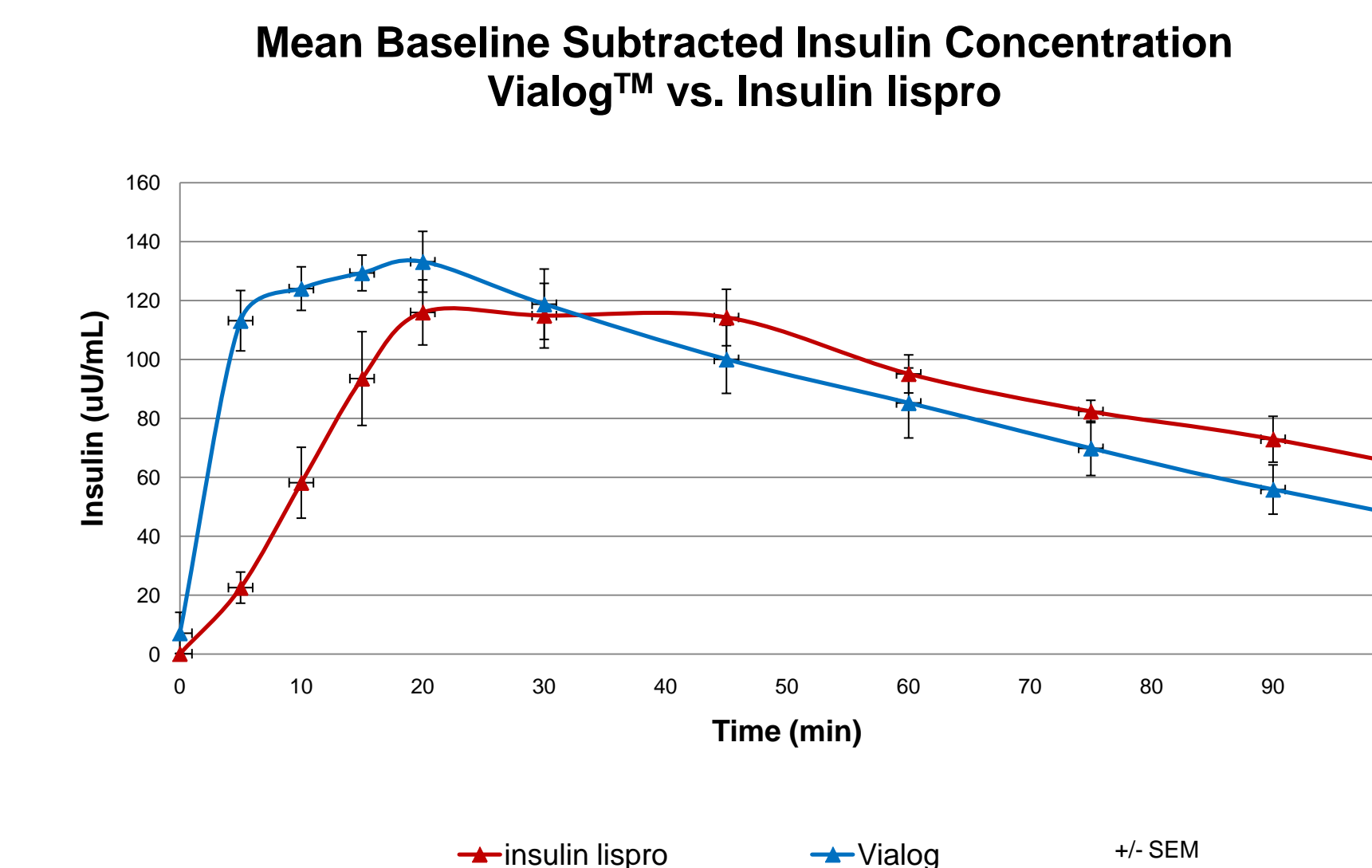


Figure 2A

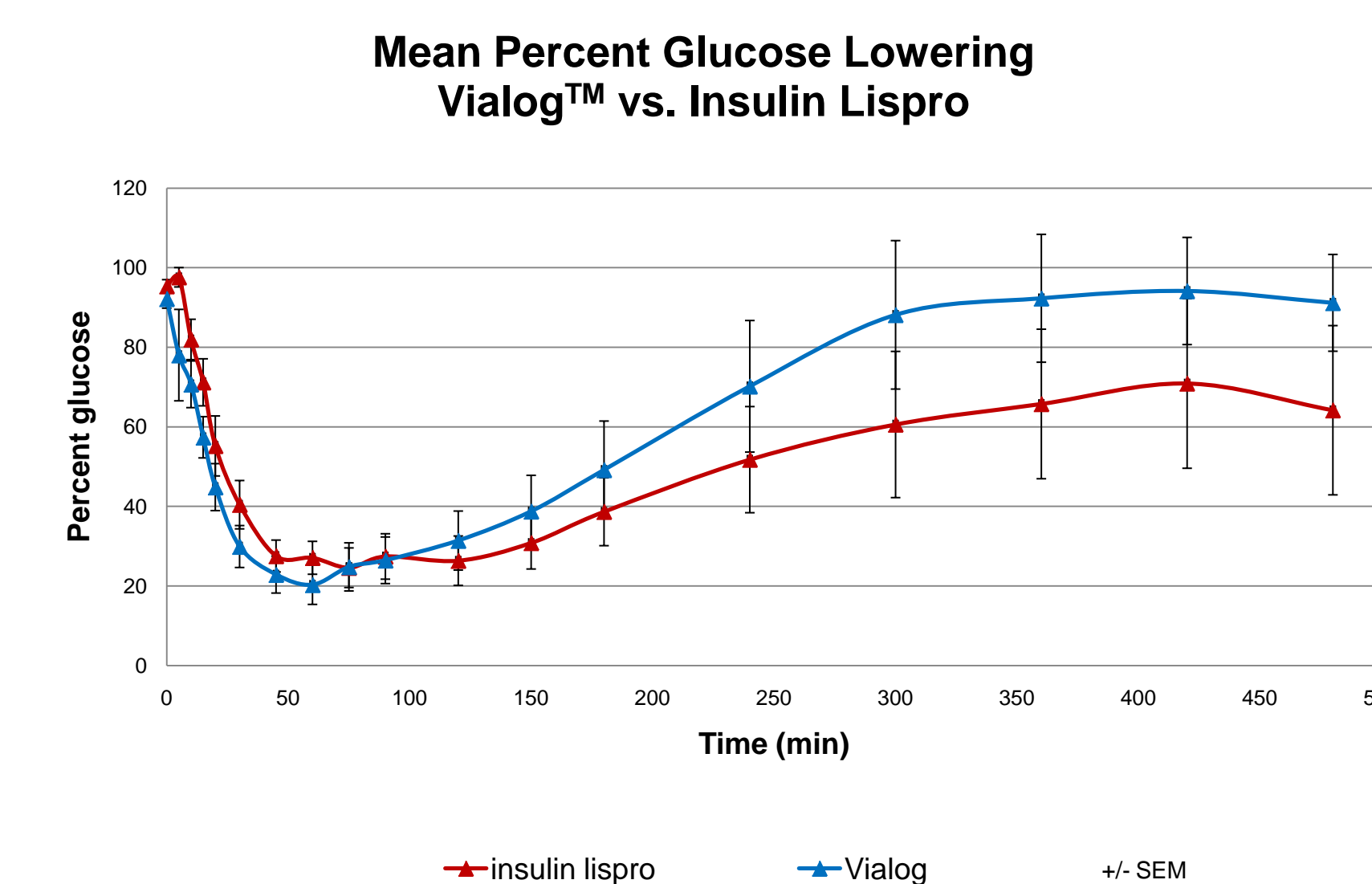


Figure 2B

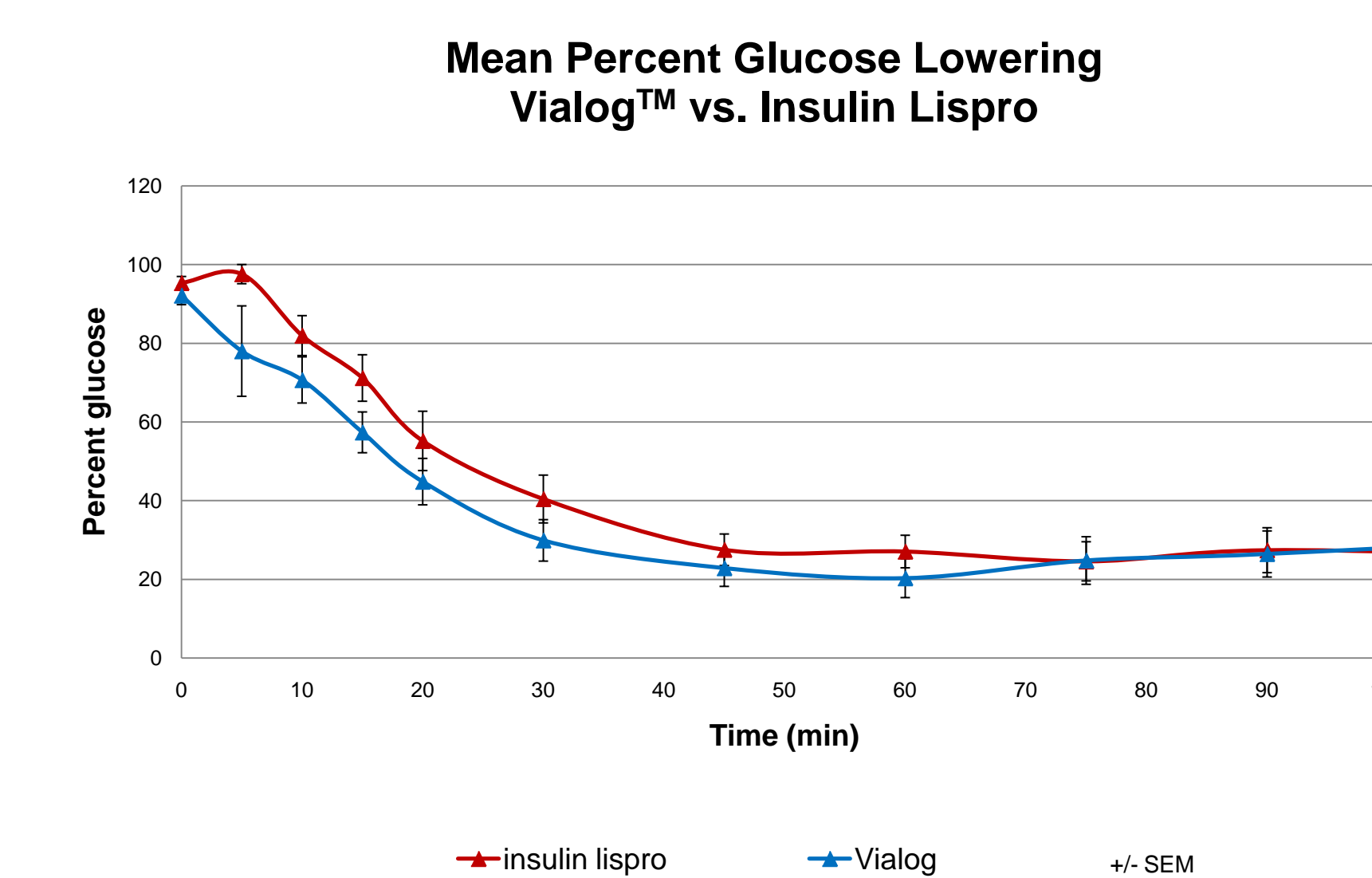


Table 1

+/- SEM	Pharmacokinetics			Pharmacodynamics		
	½ T _{max} early (min)	T _{max} (min)	½ T _{max} late (min)	Time to 20 point drop (min)	Time to ½ drop (min)	Time to nadir (min)
Vialog™	4.5 ± 1.0**	26.2 ± 6.4	78.6 ± 9.8***	8.75 ± 1.3	13.0 ± 2.0*	54.4 ± 4.9
Insulin lispro	11.7 ± 1.1	30.0 ± 6.12	111.5 ± 10.3	10.0 ± 0.9	20.7 ± 2.6	136.9 ± 50.3

*p<0.01, **p< 0.005, ***p<0.001 vs. insulin lispro

References

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