Pharmacodynamics, Pharmacokinetics and Variability of Viaject™: A Novel, Rapid-Acting Regular Human Insulin, Tested by the Glucose Clamp Technique in Patients with Type 1 Diabetes and Healthy Normals

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ABSTRACT SUMMARY: Pharmacodynamics, pharmacokinetics, and variability of the rapid-acting insulin formulation Viaject™ in normal and Type 1 diabetic patients were evaluated in clinical studies using the glucose clamp technique. Time-action profiles of SC injection indicated a very rapid rise in glucose consumption and peak metabolic activity, with less variability than regular insulin.

INTRODUCTION: Insulin molecules in most commercial formulations exist as six-molecule aggregates (hexamers), stabilized by two zinc atoms. Once injected into subcutaneous tissue, the hexamers must first dissociate into complexes of two molecules (dimers) and then into single molecules (monomers) before significant absorption of insulin into the bloodstream can occur. Viaject™ is a new formulation of recombinant human insulin**.** Rather than making an insulin analog and altering the molecule, Viaject™ contains ingredients that are generally regarded as safe (GRAS) for parenteral administration. One of these ingredients pulls the zinc ions away from the insulin, causing the insulin to dissociate**.** Another ingredient masks the charge of the insulin. Together they cause insulin to favor the monomeric form, hastening its absorption from subcutaneous tissue. The charge masking effects further increase the rate of absorption. Because the pharmaceutical active, insulin, is an already approved and well studied molecule and the formulation ingredients are GRAS, Viaject™ insulin may be approved in the next one to three years. Results from two clinical trials have established that Viaject™ is rapidly absorbed and eliminated, reducing the chance of hypoglycemic events.

EXPERIMENTAL METHODS:
In the first study, five euglycemic glucose-clamps (Biostator; target value 90 mg/dl) were performed in each of 10 fasting healthy volunteers (Average age 40 (20-62) years; BMI 22.5 (19.2-24.9) kg/m²). Using a cross-over design with a fixed treatment order, 12 IU regular human insulin (RI),12 U insulin Lispro and 12, 6, and 3 U Viaject™ were injected subcutaneously in the abdominal region. Statistics were generated using SAS.

In the second study, six euglycemic glucose clamps were performed on each of 14 Type 1 diabetic patients (average BW 78.1 kg, range 65.5-99.8 kg). On six separate occasions, separated by a minimum of 5 days, participants received three 0.1 U/kg doses of Viaject™ and three 0.1 U/Kg of RI. Investigators were blinded to the order of dosing. Paired two sample t-test functions were performed separately on insulin concentration and glucose infusion rate (GIR) results. Results were considered significant at $p<0.05$ on a two sided test.

RESULTS AND DISCUSSION:
In the first study, SC injection of Viaject™ resulted in a time-action profile that was characterized by a very rapid rise in glucose consumption even when compared to Lispro (early ½ GIR Tmax, see Table). Maximal metabolic activity was observed earlier (GIR Tmax) with Viaject™ than with Lispro or RI. The decline in metabolic action was comparable between Viaject™ and Lispro, and faster with Viaject™ than with regular human insulin. Maximal (GIR max) and total metabolic activity (GIR AUC $_{0\text{-}480}$) were comparable for all three insulin formulations. The data show that GIR $AUC_{0\text{-}120}$ for 12U Viaject™ is greater than that for 12U RI, and GIR $AUC_{0\text{-}120}$ for 6 U Viaject™ is greater than that for 12 U RI. This suggests that a meal typically requiring a dose of 12U RI could be covered by one half to one third the dose of Viaject™, with a reduced risk of hypoglycemia.

A clear dose-response relationship was observed with the three doses of Viaject™ with respect to both serum insulin levels and metabolic activity. The PK data confirm the PD results. No clinically significant adverse events were observed.

PD (mean ± SD)	early 1/2 GIR T_{max} (min)	GIR T_{max} (min)	GIR-AUC $_{0\text{-}120}$ (mg*min/kg)
Regular insulin 12U (RI)	66 ± 15	193 ± 57	571 ± 175
Insulin Lispro 12U (L)	51 ± 13 *(RI)	152 ± 30 *(RI)	775 ± 174 *(RI)
Viaject™ 12U (VJ12)	33 ± 17 *(L,RI)	137 ± 57 *(RI)	908 ± 300 *(RI)
Viaject™ 6 U (VJ6)	35 ± 18 *(L,RI)	115 ± 33 *(L,RI)	712 ± 260 *(VJ12,L)
Viaject™ 3 U (VJ3)	31 ± 14 *(L,RI)	112 ± 40 *(L,RI)	518 ± 259 *(VJ6,VJ12,L)

*(comparator) Duncan's multiple range test, $p<0.5$

Preliminary statistical analysis of the second Viaject™ study demonstrated that:

- the time to maximal insulin concentration (Tmax) was of shorter duration for Viaject™ than for RI (32.4 vs.117.9 min., $P < 0.0001$).
- the inter-subject variability of Viaject™ Tmax was statistically less than that of RI (Viaject mean SD ±15.6 min., RI mean SD ±30.8 min., $P < 0.05$).

The maximal insulin concentration (Cmax) and the inter-subject variability of Cmax were not statistically different for Viaject™ and RI.

The pharmacodynamics data from the second glucose clamp study performed in Type 1 diabetic patients were expressed in terms of GIR. Again, the time to maximal activity (GIR Tmax) and late half maximal activity were significantly shorter for Viaject™ and maximal activity (GIRmax) of Viaject™ was statistically greater in comparison to RI.

CONCLUSIONS:

The results from the first clinical study showed that the pharmacodynamic effects of Viaject™, a formulation of regular human insulin, are significantly faster than those of regular human insulin or rapid-acting insulin analogues.

In the second study, Viaject™ was repeatedly administered to patients with Type 1 diabetes. The Tmax of Viaject™was significantly faster and less variable than the Tmax of these same patients who received RI. The proven rapid action of this formulation reinforces the conclusion that Viaject™ may be a safer and more convenient prandial insulin than RI.

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