Comparative Pharmacokinetics and Insulin Action for Three Rapid-Acting Insulin Analogs Injected Subcutaneously With and Without Hyaluronidase

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OBJECTIVE—To compare the pharmacokinetics and glucodynamics of three rapid-acting insulin analogs (aspart, glulisine, and lispro) injected subcutaneously with or without recombinant human hyaluronidase (rHuPH20).

RESEARCH DESIGN AND METHODS—This double-blind six-way crossover euglycemic-glucose-clamp study was conducted in 14 healthy volunteers. Each analog was injected subcutaneously (0.15 units/kg) with or without rHuPH20.

RESULTS—The commercial formulations had comparable insulin time-exposure and time-action profiles as follows: 50% exposure at 123–131 min and 50% total glucose infused at 183–186 min. With rHuPH20, the analogs had faster yet still comparable profiles: 50% exposure at 71–79 min and 50% glucose infused at 127–140 min. The accelerated absorption with rHuPH20 led to twice the exposure in the first hour and half the exposure beyond 2 h, which resulted in 13- to 25-min faster onset and 40- to 49-min shorter mean duration of insulin action.

CONCLUSIONS—Coinjection of rHuPH20 with rapid-acting analogs accelerated insulin exposure, producing an ultra-rapid time-action profile with a faster onset and shorter duration of insulin action.

RAPID-ACTING INSULIN ANALOGS WITH ACCELERATED INSULIN ABSORPTION AND METABOLIC EFFECT RELATIVE TO REGULAR HUMAN INSULIN HAVE BEEN INTRODUCED OVER THE PAST 15 YEARS (1–3). THESE PRODUCTS ALLOW IMPROVED CONTROL OF POSTPRANDIAL HYPERGLYCEMIA AND REDUCE RISK FOR NOCTURNAL HYPOGLYCEMIA (4,5). EVEN THESE RAPID-ACTING ANALOGS ARE TOO SLOW TO ALLOW OPTIMUM GLYCEMIC RESPONSE WHEN PRANDIAL INSULIN INJECTION OCCURS IMMEDIATELY BEFORE A MEAL AND A MEAL DELAY OF 20 MIN OR MORE IS REQUIRED TO OPTIMIZE POSTMEAL GLYCEMIC RESPONSE (6,7). IN RESPONSE, NEW ULTRA-RAPID INSULIN PRODUCTS ARE UNDERGOING DEVELOPMENT (8).


RESEARCH DESIGN AND METHODS—This double-blind, six-way crossover study was conducted in 14 healthy fasting volunteers. The active comparators were Humolog (Lilly), insulin aspart injection (NovoLog; Novo Nordisk), and insulin glulisine injection (Apidra; sanofi-aventis). Investigational drugs were prepared by diluting each to 95 U/mL with rHuPH20 for a final concentration of 5 μg rHuPH20/mL. All study drugs were injected subcutaneously (0.15 units/kg) in the abdomen in random sequence. Eight-hour euglycemic glucose clamps and statistical analyses were conducted as previously described (11,12) and are described in detail (Fig. 1). Mean duration of action, which is the equivalent glucose infusion measure to mean residence time for PK curves, measures the arithmetic mean or first moment of the glucose infusion rate (GIR) as a function of time curve, and like mean residence time is calculated as the area under the first-moment curve (product of time and GIR as a function of time) divided by the area under the GIR curve (total glucose infused).

RESULTS—Fourteen subjects were enrolled and completed all six dosing visits. The subjects had a mean ± SD age of 34 ± 9 years and BMI 24.7 ± 1.5 kg/m². Eight subjects were male. Ten were white, two were black, one was Asian, and one was Pacific Islander. Adverse events in this study were generally mild, primarily procedure related, and occurred at a similar low frequency regardless of the treatment. All injections were well tolerated, and no events were considered causally related to study drug exposure.

Total exposure was comparable with or without rHuPH20. Geometric mean ratios (90% confidence interval [CI]) were 87% (90% CI 80–93%), 97 (90% CI 92–101%), and 101 (90% CI 97–104%) for lispro, aspart, and glulisine, respectively, here and in subsequent listings. None of the differences was statistically significant, and because the 90% CIs for each analog with rHuPH20 were within the 80–125% range of control, the total exposure with or without rHuPH20 is considered bioequivalent (13).

Insulin exposure was accelerated for all three analogs with rHuPH20 (Fig. 1). Time to 50% exposure (mean ± SD) was decreased from approximately 2 h for the
Figure 1—Cumulative exposure and action of insulins glulisine, lispro, and aspart after subcutaneous injection with and without rHuPH20. Blood samples were collected on each dosing day at 30, 20, and 10 min before and 3, 6, 9, 12, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, 360, 420, and 480 min after injection of each study drug for the measurement of serum insulin samples using a conventional competitive radio-immunoassay (Millipore, St. Charles, MO) using broad-spectrum antiserum (catalog 1013-K; Millipore) that binds each of the analogs and human insulin and was validated for each of the analogs individually. A Biostator was used to clamp blood glucose at 90% fasting level to suppress endogenous insulin production with tight blood glucose control (individual clamp glucose SDs were between 3.5 and 6.8 mg/dL). Results are displayed as a cumulative percent of the total exposure (left panel; see text for total exposure) and total glucose infused (right panel; mean ± SD total glucose infused were 1.7 ± 0.6, 1.7 ± 0.6, 1.8 ± 0.5, 1.7 ± 0.5, 1.9 ± 0.5, and 1.4 ± 0.5 for glulisine, glulisine plus rHuPH20, lispro, lispro plus rHuPH20, aspart, and aspart plus rHuPH20, respectively).

The faster insulin PK led to an accelerated time-action profile for each analog when injected with rHuPH20 (Fig. 1). The approximately 45-min acceleration of insulin exposure was mirrored with a corresponding acceleration of time to 50% glucose infused from approximately 3 h when injected alone to just more than 2 h with rHuPH20 (183 ± 34 to 135 ± 28, 186 ± 38 to 140 ± 28, and 186 ± 34 to 127 ± 32 min; all P < 0.0001). The peak exposure (C_max) was greater and earlier (t_max) when each analog was injected with rHuPH20 (P < 0.0001 unless noted); geometric mean C_max ratios were 158, 210, and 187%, and t_max was reduced from 80 to 41, from 68 to 41 (P = 0.0032), and from 86 to 44 min. Early (first-hour) exposure was doubled with rHuPH20 (geometric ratios: 208, 291, and 266%) and halved beyond 2 h (58, 53, and 41%; all P < 0.0001).

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CONCLUSIONS—The acceleration of insulin PK and time-action profiles by coinjection with rHuPH20 observed in this study confirms the results of previous studies with regular human insulin and lispro (8,10,11) and extends these findings to insulins aspart and glulisine. The ultra-rapid profiles described here could have benefits improving control of postprandial glycemic excursions, and administration of lispro plus rHuPH20 has been shown to reduce postprandial hyperglycemia relative to lispro alone dosing immediately before liquid meals in patients with type 1 and type 2 diabetes (14,15). Studies are currently underway to compare the utility of ultrafast aspart plus rHuPH20 and lispro plus rHuPH20 drug products with commercial Humalog as part of intensive basal-bolus insulin therapy in the treatment of type 1 and type 2 diabetes (NCT01194245 and NCT01194258, clinicaltrials.gov).
L.M., D.B.M., and M.H. conducted the study. D.B.M. and D.E.V. conceived the study. L.M., D.B.M., M.H., E.A.L., and D.E.V. designed the study, analyzed and interpreted the results, and contributed to the review and revision of the study. D.E.V. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References