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Letter to the Editor

Pharmacokinetics and Glucodynamics of Rapid-, Short-, and Intermediate-Acting Insulins: Comparison of Jet Injection to Needle Syringe

Dear Editor:

Insulin-requiring diabetes, whether resulting from type 1 or from progression of type 2 disease, requires strict attention to glycemic control in order to reduce the incidence of micro- and macrovascular complications. To approach the goal of euglycemia, individualized patient treatment may demand an intensive regimen, which can negatively impact patient compliance due to the "fear factor" or inconvenience of use of needle syringes. Additionally, the hazards of needle-stick accident in institutional and private use settings have become an increasing health issue due to potential transmission of blood-borne pathogens.[1,2]

As an alternative to use of syringes, jet injectors were developed in the 1940s and were implemented for mass inoculations. Recently, state and federal legislation has encouraged development of safer injection products, and jet injection technology has gained momentum in multiple clinical areas as a result. The Injex device is a Food and Drug Administration-cleared needle-free jet injector. It utilizes a spring mechanism to propel 0.05–0.3 mL of solution through a 0.007-inch orifice with sufficient force to enter the subcutaneous tissue to a depth equivalent to standard needle syringe. The device utilizes a low-cost, single-use disposable cartridge, which minimizes the potential for cross-contamination. Recently, the Injex has been shown to safely and efficaciously deliver the measles, mumps, and rubella vaccine (MMR_{II}) in a cohort of pediatric subjects.[3]

Despite the long history of jet injectors there have been few studies of insulin administration and fewer studies still of the pharmacokinetics of insulins delivered via jet injection. Of those studies that have been performed, there have been observations of more rapid absorption[4] and increased area under the insulin concentration–time curve[5] when compared with needle syringe. The present study employs the euglycemic clamp technique[6,7] in a cohort of healthy volunteers as a model for insulin effects in patients with diabetes. The main objective of the study is to evaluate the pharmacokinetics and glucodynamics of various insulins delivered via needle syringe and the Injex jet injector.

METHODS

Under approval from an institutional review board, we studied a cohort comprising 12 males and four females. The cohort ethnic distribution included seven Caucasians, seven African-Americans, and two subjects of Asian descent. Mean subject age was 40 ± 8 years, and mean body mass index was 23 ± 2 kg/m^2. Gender-specific mean body weights were 59 ± 8 kg (females) and 74 ± 7 kg (males).

Study design

Each member of the cohort of 16 subjects was assigned in groups of four to one of four study arms: Arm 1 received rapid-acting insulin lispro (Humalog); arm 2 received short-acting regular insulin (Humulin-R); arm 3 received intermediate-acting NPH (Humulin-N); and arm 4 received premixed insulin (Humulin 70/30).

Each subject received bolus 30 unit insulin injections in random order with either the Injex 30 jet injector (Equidyne Systems, San Diego, CA) or a 0.5-mL syringe with a 28-gauge needle (Becton-Dickinson, Franklin Lakes, NJ). To establish and maintain a euglycemic clamp, 20% dextrose (Baxter Healthcare, Deerfield, IL) was supplied via infusion pump. Glucose levels were monitored throughout the clamp procedure, and the glucose infusion rate (GIR) was manually adjusted to maintain euglycemia at basal levels.

Blood samples were taken for plasma insulin measurements at predose and 15, 30, 45, 60, 90, 120, 240, and 360 min postinjection for subjects receiving lispro; predose and 30, 60, 120, and 480 min for regular insulin; and predose and 120, 240, 360, and 600 min for NPH and 70/30. Plasma glucose was determined via the glucose oxidase method. Plasma insulin was measured by competitive inhibition radioimmunoassay. The limit of quantification was 1.0 μU/mL.

Pharmacokinetic, glucodynamic, and statistical methods

Model-dependent pharmacokinetic analysis was applied to all plasma insulin concentration–time data. The maximum concentration (C_{max}), corresponding time (t_{max}), half-life ($t_{½}$), elimination rate constant (KELIM), area under the curve from time 0 to last sampling ($AUC_{0\text{-}t}$), and volume of distribution (V_d) were determined. Glucodynamic parameters including maximum infusion rate (R_{max}) and corresponding time (TR_{max}) were determined directly from infusion rate logs for each subject. To investigate the significance of differences in pharmacokinetic and glucodynamic parameters by device, the paired t test was utilized ($p < 0.05$ was considered significant).

RESULTS

Pharmacokinetic results

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Pharmacokinetic parameters by insulin type and device are summarized in Table 1. In the insulin lispro arm, the time to maximal concentration (t_{max}) is significantly shorter with the jet injector (41 min vs. 85 min for needle syringe, $p < 0.05$). Mean C_{max} in the NPH study arm is approximately 45% higher with the jet injector than with the syringe and approaches but does not attain significance ($p = 0.05$). V_d in the NPH study arm is significantly lower with jet injection (274 L) than with syringe (434 L). In all comparisons, the results for elimination $t_{½}$, KELIM, and $AUC_{0\text{-}t}$ are essentially equivalent for jet injector and needle syringe.

Glucodynamics

Peak GIR (R_{max}) and time to peak effect (TR_{max}) by insulin and device type are presented in Table 1. The TR_{max} is significantly shorter ($p < 0.05$) for regular insulin administered via jet injector (173 min vs. 290 min for syringe). There is also a general trend for shorter TR_{max} for insulin lispro, NPH, and 70/30 insulins delivered by jet injector, suggestive of a more rapid glucose-lowering effect. There were no statistically significant differences by insulin and injector type for R_{max}, indicating that the peak glucose-lowering effects of administered insulins were equivalent between jet injector and needle syringe.

DISCUSSION

The results of this study demonstrate minimal differences in pharmacokinetic and glucodynamic properties of exogenous insulins delivered via jet injection in comparison with needle syringe. The most intriguing metabolic difference is a slightly more rapid glucose-lowering effect following jet injection of rapid- and short-acting insulins. All other parameters are essentially equivalent. Thus, the Injex device may provide a safe and effective alternative to needle delivery. This could be helpful in increasing patient compliance, which may result in improved metabolic control. Moreover, reductions in diabetic complications may have far-reaching healthcare economic benefits.[8,9] Further, patients with insulin-induced lipoatrophy may observe reduced lesion incidence and severity following adaptation to jet injection.[10]

Table 1. Pharmacokinetic and Glucodynamic Results by Insulin Type and Device

	Insulin lispro		*Regular insulin*		*NPH*		*70/30*	
	Injex	*Syringe*	*Injex*	*Syringe*	*Injex*	*Syringe*	*Injex*	*Syringe*
C_{max} (μU/mL)	108 (21)	74 (27)	45 (23)	65 (27)	48 (6)	33 (10)	42 (16)	32 (6)
t_{max} (min)	41 (15)	85 (14)[1]	67 (35)	68 (40)	233 (42)	221 (88)	195 (80)	220 (46)
$t_{1/2}$ (min)	123 (71)	193 (177)	302 (210)	242 (228)	434 (378)	661 (523)	272 (284)	294 (285)
KELIM (/min)	0.007 (0.003)	0.007 (0.005)	0.004 (0.004)	0.005 (0.003)	0.002 (0.001)	0.002 (0.001)	0.005 (0.003)	0.008 (0.01)
V_d (L)	199 (55)	204 (94)	469 (302)	251 (140)	274 (34)	434 (120)[1]	336 (340)	305 (234)
$AUC_{0\text{-}t}$ (μU-min/mL)	23,347 (8,172)	25,498 (7,505)	24,263 (17,520)	31,333 (12,581)	45,609 (29,832)	39,641 (30,934)	26,295 (9,833)	31,481 (12,409)
GIR								
R_{max} (mL/h)	266 (34)	274 (26)	136 (84)	219 (77)	212 (84)	141 (89)	155 (77)	153 (74)
TR_{max} (min)	131 (95)	181 (49)	173 (63)[1]	290 (61)	320 (70)	348 (112)	320 (67)	348 (57)

Thirty units of each insulin was subcutaneously administered via jet injector or needle syringe to healthy subjects under euglycemic clamp conditions. Blood glucose was monitored every 5 min, and the GIR was adjusted manually. Plasma insulin was measured via specific radioimmunoassay. Data are means (SD).

[1]$p < 0.05$ versus Injex.

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REFERENCES

1. Cardo DM, the Centers for Disease Control and Prevention Needle Stick Surveillance Group: A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med 1997;337:1485–1490.
2. Simonsen L, Kane A, Lloyd J, Zaffran M, Kane MZ: Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. Bull WHO 1999;77:10:789–800.
3. Sarno MJ, Blase E, Galindo N, Ramirez R, Schirmer C, Trujillo-Juarez DF: Clinical immunogenicity of measles, mumps, and rubella vaccine delivered by the Injex jet injector: comparison with standard syringe injection. Pediatr Infect Dis J 2000;19:9:839–842.
4. Kerum G, Profozic V, Granic M, Skrabalo Z: Blood glucose and free insulin levels after the administration of insulin by conventional syringe or jet injector in insulin treated type 2 diabetes. Horm Metab Res 1987;19:9:422–425.
5. Malone JI, Lowitt S, Grove NP, Shah SC: Comparison of insulin levels after injection by jet stream and disposable insulin syringe. Diabetes Care 1986;9:6:637–640.
6. Bratusch-Marrain PR: The euglycemic insulin and hyperglycemic clamp technic. Methods for the determination of insulin sensitivity of tissues and glucose sensitivity of the B cell. Infusionsther Klin Ernahr 1984;11:4–10.
7. Rave K, Heise T, Weyer C, Herrnberger J, Bender R, Hirschberger S, Heinemann L: Intramuscular versus subcutaneous injection of soluble and lispro insulin: comparison of metabolic effects in healthy subjects. Diabet Med 1998;15:747–751.
8. Edelman SV: Importance of glucose control. Med Clin North Am 1998;82:4:665–687.
9. Edelman SV: Type II diabetes mellitus. Adv Intern Med 1998;43:449–500.
10. Logwin S, Conget I, Jansa M, Vidal M, Nicolau C, Gomis R: Human insulin-induced lipoatrophy. Successful treatment using a jet-injection device. Diabetes Care 1996;19:255–256.

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