

# Improved Pharmacokinetic and Pharmacodynamic Profile of Rapid-Acting Insulin Using Needle-Free Jet Injection Technology

E. (ELSEMIEK) E.C. ENGWERDA, BSC  
EVERTINE J. ABBINK, PHD

CEES J. TACK, PHD  
BASTIAAN E. DE GALAN, PHD

**OBJECTIVE**—Insulin administered by jet injectors is dispensed over a larger subcutaneous area than insulin injected with a syringe, which may facilitate a more rapid absorption. This study compared the pharmacologic profile of administration of insulin aspart by jet injection to that by conventional insulin pen.

**RESEARCH DESIGN AND METHODS**—Euglycemic glucose clamp tests were performed in 18 healthy volunteers after subcutaneous administration of 0.2 units/kg body wt of aspart, either administered by jet injection or by conventional pen, using a randomized, double-blind, double-dummy, cross over study design. Pharmacodynamic and pharmacokinetic profiles were derived from the glucose infusion rate (GIR) needed to maintain euglycemia and from plasma insulin levels, respectively.

**RESULTS**—The time to maximal GIR was significantly shorter when insulin was injected with the jet injector compared with conventional pen administration ( $51 \pm 3$  vs.  $105 \pm 11$  min,  $P < 0.0001$ ). The time to peak insulin concentration was similarly reduced ( $31 \pm 3$  vs.  $64 \pm 6$  min,  $P < 0.0001$ ) and peak insulin concentrations were increased ( $108 \pm 13$  vs.  $79 \pm 7$  mU/L,  $P = 0.01$ ) when insulin was injected by jet injection compared with conventional pen injection. Jet injector insulin administration reduced the time to 50% glucose disposal by  $\sim 40$  min ( $P < 0.0001$ ). There were no differences in maximal GIR, total insulin absorption, or total insulin action between the two devices.

**CONCLUSIONS**—Administration of insulin aspart by jet injection enhances insulin absorption and reduces the duration of glucose-lowering action. This profile resembles more closely the pattern of endogenous insulin secretion and may help to achieve better meal insulin coverage and correction of postprandial glucose excursions.

Administration of insulin by jet injection is a needle-free alternative to conventional insulin administration with syringes or insulin pens. Jet injectors deliver insulin at a high velocity (typically  $>100$  m/s) across the skin in the subcutaneous tissue and may dispense the insulin over a larger area than insulin injected with a syringe (1). This may enhance the efficiency with which insulin is absorbed from the subcutaneous compartment into the circulation so that the insulin peak can be advanced and the

duration of (glucose-lowering) action reduced. Studies on jet injection technology for insulin administration date back to the 1960s (2). Most have suggested faster absorption of regular and NPH insulin when injected with a jet injector rather than with a syringe (3–8). Data on the use of jet injectors for the administration of rapid-acting insulin analogs are limited to one open-label study. In that study, peak insulin levels were reached in about half the time when lispro insulin was injected with a jet injector instead of a

syringe. However, the glucose-lowering time-action profiles were not significantly different, the number of subjects examined was low ( $n = 4$ ), and the dose of insulin tested was relatively high (30 units for all) (9).

Although rapid-acting insulin analogs have clearly advanced glycemic treatment of type 1 and insulin-requiring type 2 diabetes, their pharmacological profile is still far from mimicking the profile of endogenous insulin release. Indeed, the time until insulin's maximal glucose-lowering effect generally amounts to  $>90$  min, and the duration of significant hyperinsulinemia often exceeds 3 hours (10–12). As a consequence, risks of (immediate) postprandial hyperglycemia and (late) postprandial hypoglycemia remain relatively high in many patients treated with rapid-acting insulin analogs. Faster absorption of insulin may reduce these risks and may provide a more physiological meal-time substitution of insulin. The aim of this study was therefore to compare the pharmacodynamic and pharmacokinetic profile of subcutaneous administration of the rapid-acting insulin analog aspart by jet injection to that of administration by conventional insulin pen in healthy individuals using the euglycemic glucose clamp technique (13). We chose to use an insulin pen as comparator because insulin pens may be more accurate than syringes (14) and are currently used by the vast majority of insulin-treated patients with diabetes in western Europe (15).

## RESEARCH DESIGN AND METHODS

Written informed consent was obtained from 18 healthy, non-smoking subjects (men/women 5/13, mean  $\pm$  SD age  $27.2 \pm 9.4$  years, mean BMI  $23.6 \pm 2.8$  kg/m<sup>2</sup>, mean fasting plasma glucose level  $5.09 \pm 0.35$  mmol/L) who were recruited by advertisement. None of the participants were on chronic medication (with the exception of oral contraceptives), reported type 2 diabetes among first-degree relatives, or had a history of cardiovascular events. A pregnancy

From the Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

Corresponding author: Bastiaan E. de Galan, b.degalan@aig.umcn.nl.

Received 28 January 2011 and accepted 17 May 2011.

DOI: 10.2337/dc11-0182. Clinical trial reg. no. NCT00983775, clinicaltrials.gov.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.