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

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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 ± 3 vs. 105 ± 11 min, P < 0.0001). The time to peak insulin concentration was similarly reduced (31 ± 3 vs. 64 ± 6 min, P < 0.0001) and peak insulin concentrations were increased (108 ± 13 vs. 79 ± 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 ~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.
Insulin administration by jet injection

test was performed in female subjects at the screening visit to exclude pregnancy. The study was approved by the institutional review board of the Radboud University Nijmegen Medical Centre.

Experimental study design
All participants underwent two euglycemic glucose clamp experiments (13,16) to investigate the pharmacokinetics and pharmacodynamics of rapid-acting insulin delivered by jet injection or conventional pen injection, using a double-blind, double-dummy, randomized cross over study design. There was a washout period of at least 1 week between the two clamps, whereas female subjects were tested at 4- or 8-week intervals to ensure that experiments took place during corresponding periods of the menstrual cycle.

Participants were admitted to the research unit at 0830 h after an overnight fast and having abstained from smoking, alcohol use, and caffeine use for at least 24 h. The experiments were performed in supine position in a temperature controlled room (22–24°C). Two catheters were inserted intravenously. One catheter was inserted in retrograde fashion in a dorsal hand vein for blood sampling. This hand was placed in a heated box, kept at 55°C to arterialize venous blood (17,18). The other catheter was placed in an antecubital vein of the contralateral arm for administration of 20% dextrose.

After instrumentation, a 30-min equilibration period was included before blood was sampled for baseline values of plasma glucose and plasma insulin. Subsequently, all participants received both insulin (aspart, Novo Nordisk, Bagsvaerd, Denmark) and placebo by the conventional pen were operated by trained personnel only and were prepared by a nurse who was not involved in the trial. After administration of insulin and placebo solution, plasma glucose was maintained at euglycemic levels (~5.0 mmol/L) for 8 h by a variable infusion of 20% dextrose, the rate of which was determined by plasma glucose measurements at 5-min intervals during the first 4 h and at 10-min intervals thereafter. Blood for plasma insulin levels was sampled every 10 min during the 1st hour and every 30 min for the remainder of the study.

All pharmacodynamic and pharmacokinetic study end points were derived from the exogenous glucose infusion rate (GIR) and insulin concentration profiles. The primary study end point was the time to maximal GIR (T-GIRmax), corresponding to the time until the maximal glucose-lowering effect of insulin was obtained. Secondary pharmacodynamic end points were the maximal GIR (C-GIRmax), the time to 50% of glucose disposal (T-GIR50%), and the total amount of glucose administered calculated from the area under the curve (AUC) (GIRtot).

Secondary pharmacokinetic end points included the time to maximal insulin concentration (T-INSmax), the maximal insulin concentration (C-INSmax), the area under the insulin concentration curve (INSauc), and the time until 50% of insulin absorption, calculated as 50% of the area under the insulin concentration curve (T-INSauc50%).

Analytical procedures
Plasma glucose levels were determined in duplicate, immediately after blood sampling by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA). Blood sampled for plasma insulin measurements was collected in lithium-heparin tubes and placed on ice. After centrifugation, the supernatant was stored at −20°C. Plasma insulin was measured by radioimmunoassay (19) after all experiments were performed.

Statistical analyses
Assuming a T-GIRmax of 94 min with a SD of 46 min for aspart insulin administered subcutaneously in the abdomen by conventional pen injection (10), we calculated that a total of 18 subjects would be needed to find a 20% reduction in the primary end point with 80% statistical power at the conventional P value of 0.05, after correction for small sample sizes.

All data are expressed as means ± SEM, unless otherwise indicated. Mean outcomes for all study end points were tested by paired t tests. The GIR and insulin concentration profiles were compared by ANOVA. All statistical analyses were performed by SPSS 16.0 (Statistical Package for Social Sciences, Chicago, IL). A P value of < 0.05 was considered statistically significant.

RESULTS—All 18 subjects completed the study. In two subjects, one of the clamp experiments had to be rescheduled because insulin levels failed to increase, with both incidents occurring when the jet injector contained insulin. In one instance, the jet injector was incompletely checked for air bubbles in the system. In the other instance, the spring was released before proper contact could be made with the skin, after which the jet injector was returned to the manufacturer and replaced. Injections were well tolerated by the participants, although some participants regarded the firm pressure required for injection with the jet injector as unpleasant. Neither injection mode resulted in skin reactions such as hematomas or redness. Mean plasma glucose levels during the clamps were 5.0 ± 0.1 mmol/L with both devices. The corresponding coefficients of variation were 8.0 ± 0.8% and 7.3 ± 0.5% for the jet injector and conventional insulin pen, respectively.

Pharmacodynamic end points
All results of pharmacodynamic end points are shown in Fig. 1 and listed in Table 1. The time to maximal glucose-lowering effect, as represented by T-GIRmax, was reduced by >50% when insulin was administered with the jet injector as compared with conventional insulin administration. There were no differences in maximal glucose-lowering effect (C-GIRmax) or the total amount of glucose administered (GIRtot) between the two devices. However, the time to 50% of glucose disposal (T-GIR50%), representing the total duration of insulin action, was approximately 40 min shorter for insulin administration by jet injector than by conventional insulin pen.
Pharmacodynamic parameters

Insulin administered with the jet injector was absorbed faster into the circulation, resulting in a more immediate onset, ensuring a more immediate effect in comparison with conventional insulin administration. In addition, insulin administration by jet injection reduced the total duration of hyperinsulinemia and insulin action by 30–40 min when compared with conventional insulin administration. There were no indications that these benefits of the jet injector over the conventional pen differed between women and men.

Our data are in line with previous studies that have shown a more rapid increase in insulin levels and shorter duration of hyperinsulinemia after administration of regular insulin by jet injection compared with administration by needle syringe (3–8). The results of the current study also extend those of a recent study performed by Sarno et al. (9), who compared administration of various insulins (including lispro insulin) with jet injection to that with needle syringes. In that study, time to peak insulin levels after lispro insulin administration was shorter for the jet injector than for needle syringe injection, but a statistically significant pharmacodynamic effect could not be established. Also, the number of volunteers examined was small (n = 4) and the dose of insulin used was fixed at a relatively high level (30 units for all). Our study convincingly shows the pharmacokinetic and pharmacodynamic superiority of jet injection over conventional needle pens for administration of rapid-acting insulin at a dose that is realistic for many people with type 1 or type 2 diabetes. It is also the first time that jet injection technology was compared with an insulin pen, which most patients prefer over syringes for their ease of use and high level of accuracy (20).

Insulin injected by jet injection displays a specific cone-like dispersion pattern in the subcutaneous tissue with a relatively large surface area (1,2). It seems plausible that this dispersion pattern enhances absorption of insulin into the circulation, thus explaining a more immediate glucose-lowering effect. The current jet injector uses a high-velocity jet that ensures >90% delivery of injected insulin into the subcutaneous tissue, without risking penetration of the underlying muscle, at a jet stream diameter of ~0.15 mm. These device characteristics compare favorably to the length and diameter of pen needles that typically measure 6–8 mm and 0.5 mm, respectively. A limitation to the use of jet injectors in comparison with insulin pens is that sufficient training is required with both air-free

Pharmacokinetic end points

The results of pharmacokinetic end points are also listed in Table 1. In analogy with the pharmacodynamic results, the time to reach peak insulin levels was reduced by more than 50% after jet injector insulin administration as compared with insulin administration with the conventional pen. Insulin administered with the jet injector also resulted in higher peak insulin levels (C-INS_{max}) than insulin administered with the conventional insulin pen (Fig. 2). The INS_{AUC} did not differ between the jet injector and the conventional insulin pen, but T-INS_{AUC50%} was significantly shorter for the jet injector, indicating faster insulin absorption from the subcutaneous tissue into the circulation.

There was no indication that sex modified the pharmacodynamic or pharmacokinetic differences between the jet injector and conventional pen for insulin administration. In fact, the jet injector performed significantly better than the conventional pen in both groups, when analyzed separately (data not shown but available upon request).

CONCLUSIONS—In this study, the pharmacodynamic and pharmacokinetic profiles of the rapid-acting insulin analog aspart, injected by either jet injection technique or by conventional insulin pen, were compared. We found that the jet injector greatly enhanced the rate of insulin absorption, resulting in a truly immediate onset of action and approximately halving of the time to reach maximal glucose-lowering effect in comparison with conventional insulin administration.

Table 1—Pharmacokinetic and pharmacodynamic parameters for insulin administration with the jet injector and the conventional insulin pen

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Jet injector</th>
<th>Conventional insulin pen</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-INS_{max} (min)</td>
<td>31 ± 3</td>
<td>64 ± 6</td>
<td>&lt;0.0001</td>
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<tr>
<td>C-INS_{max} (mU/L)</td>
<td>108 ± 13</td>
<td>79 ± 7</td>
<td>0.012</td>
</tr>
<tr>
<td>INS_{AUC} (unit · min^{-1} · mL^{-1})</td>
<td>14.6 ± 1.6</td>
<td>15.2 ± 1.4</td>
<td>0.53</td>
</tr>
<tr>
<td>T-INS_{AUC50%} (min)</td>
<td>111 ± 5</td>
<td>147 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pharmacodynamic parameters</td>
<td></td>
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<tr>
<td>T-GIR_{max} (min)</td>
<td>51 ± 3</td>
<td>105 ± 11</td>
<td>0.0001</td>
</tr>
<tr>
<td>C-GIR_{max} (mg · kg^{-1} · min^{-1})</td>
<td>6.49 ± 0.58</td>
<td>6.09 ± 0.56</td>
<td>0.50</td>
</tr>
<tr>
<td>GIR_{tot} (g)</td>
<td>70.0 ± 6.9</td>
<td>83.3 ± 9.8</td>
<td>0.19</td>
</tr>
<tr>
<td>T-GIR_{SP50%} (min)</td>
<td>123 ± 7</td>
<td>1.66 ± 6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Insulin administration by jet injection

Figure 2—Mean plasma insulin levels after administration of rapid-acting insulin by the jet injector (closed symbols, black line) or the conventional insulin pen (open symbols, dashed line) during the euglycemic glucose clamp.

filling of the injection chamber and the injection procedure itself. We had to re-schedule the first experiment, probably because of an air bubble in the system, and another experiment because of early discharge of the spring system, possibly related to failure of the lock/release system. However, after proper training, administration of the entire dose of insulin can be achieved in almost all instances (21).

The pharmacokinetic and pharmacodynamic profile of rapid-acting insulin administered by the jet injector approached the physiological pattern of endogenous insulin secretion and subsequent glucose-lowering response more closely than insulin administered by a conventional insulin pen. Consequently, a more physiological meal insulin substitution may decrease immediate postprandial hyperglycemia, whereas the more rapid tapering of hyperinsulinemia may reduce the risk of late postprandial hypoglycemia. Faster insulin action may also advance correction of erratic hyperglycemia. These effects are clinically relevant for patients aiming for strict glycemic control. However, postprandial glucose may contribute less to overall glycemic control than preprandial glucose in patients with diabetes, and the role of postprandial hyperglycemia as an independent cardiovascular risk factor is still uncertain (22).

Therefore, appropriately designed studies are needed to determine whether and to what extent the favorable pharmacologic properties of insulin administration by jet injection found in this study translate into clinical benefit in the longer term for patients with diabetes.

A strength of our study is the use of a double-dummy cross-over study design, ensuring that both participants and investigators were truly blinded during the execution of the experiments. This contrasts with previous studies on jet injectors. Moreover, because we used a placebo solution that contained the same ingredients as the insulin solution (except for insulin), the smell and viscosity of the two liquids were indistinguishable. A limitation of this study is that the euglycemic clamps were performed in healthy individuals rather than in patients with diabetes, the target population for such a device. In addition, only one insulin dose was investigated; it cannot be determined with certainty whether the current differences in time-action profiles can be extrapolated to other insulin doses. Finally, the ease of use of the jet injector was not tested, which is important for a device that is aimed at being used on a daily basis.

In conclusion, the current study shows that when insulin is administered with a jet injector instead of a conventional insulin pen, a more rapid onset of insulin action can be achieved. Insulin administered by the jet injector resembles the pattern of endogenous insulin secretion more closely and could therefore be useful in providing a more physiologic postprandial insulin profile. Future research will need to investigate whether these results can be replicated in patients with diabetes and what the clinical implications are.

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E.E.C.E. performed the experiments, analyzed and interpreted data, wrote the manuscript, and reviewed and edited the manuscript. E.J.A. wrote the study protocol, performed the experiments, analyzed and interpreted data, and reviewed and edited the manuscript. C.J.T. designed the study, interpreted data, and reviewed and edited the manuscript. B.E.D.G. designed the study, wrote the study protocol, performed the experiments, analyzed and interpreted data, and reviewed and edited the manuscript.

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