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Body mass index and the efficacy of needle-free jet injection for the administration of rapid-acting insulin analogs, a *post hoc* analysis

We recently showed in a euglycaemic glucose clamp study among 18 healthy volunteers that using jet injectors rather than conventional pens significantly improved the time-action profiles of rapid-acting insulin analogs. Here, we investigated whether such profiles were modified by body mass index (BMI) and related weight parameters by comparing insulin administration by jet injection to that by conventional pen in subgroups defined by BMI, waist-to-hip ratio, waist circumference and insulin dose. After conventional administration, times to peak insulin levels ($T\text{-}INS_{max}$) occurred 31.1 [95% confidence interval (CI) 13.7–48.5] min later and time to maximum glucose requirement ($T\text{-}GIR_{max}$) 56.9 (95%CI 26.6–87.3) min later in more obese (BMI > 23.6 kg/m^2) than in lean subjects (BMI < 23.6 kg/m^2). In contrast, $T\text{-}INS_{max}$ and $T\text{-}GIR_{max}$ were similar in subjects with high and low BMI, when insulin was administered by jet injection. We conclude that using jet injection for insulin administration may especially benefit subjects with higher body weight.

Keywords: body mass index/obesity indices, euglycaemic glucose clamp, insulin administration, insulin analogs, insulin aspart, jet injector, pharmacodynamics, pharmacokinetics

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RESEARCH LETTER

Introduction

Most studies investigating the pharmacology of rapid-acting insulin analogs have been conducted in lean subjects, whereas many patients with type 1 and the majority of patients with insulin-requiring type 2 diabetes are overweight or obese. A high body mass index (BMI) may considerably delay the absorption rate and onset of action of regular insulin [1–3] and possibly that of rapid-acting insulin analogs. Such delays may be due to greater thickness of the subcutaneous tissue at the (abdominal) injection site or because higher insulin doses are required [4]. A delay in insulin absorption rate may exacerbate postprandial hyperglycaemia and, because the proportional contribution of postprandial glucose to the HbA1c increases with lower HbA1c values, interfere with the aim for tight glycaemic control [5].

In a recent study, we showed that jet injectors, which deliver insulin by means of air pressure instead of a needle, significantly advanced the time-action profile of the rapid-acting insulin analog aspart [6]. Jet injection results in a distinct spray-like dispersion pattern that ensures a larger absorptive area and faster penetration through the subcutaneous tissue compared to conventional administration by syringes or pens [7]. We hypothesized that the impact of adiposity on insulin absorption may be less when insulin is administered by jet injection. To test this hypothesis, we performed a *post hoc* analysis to assess whether BMI and other body weight parameters modified the pharmacology of insulin injected by jet injection.

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Materials and Methods

Participants

Non-smoking healthy adults, aged 18–50 years and with a BMI of 18–28 kg/m^2 were enrolled and asked to provide written informed consent. The study was approved by the institutional review board of the Radboud University Nijmegen Medical Centre.

Experimental Study Design

The research protocol has been described in detail previously [6]. Briefly, all participants underwent two 8-h euglycaemic glucose clamps, using a randomized, controlled, double-blind, double-dummy, cross-over study design. Venous catheters were placed for administration of dextrose 20% and frequent blood sampling. Insulin aspart (Novo Nordisk, Bagsvaerd, Denmark) at a dose of 0.2 U/kg body weight and a comparable volume of placebo solution (Test Medium Penfill®; Novo Nordisk) were then simultaneously injected subcutaneously on both sides of the lower abdomen. On one occasion, insulin was administered by the jet injector (Insujet™; European Pharma Group, Schiphol Rijk, the Netherlands) and placebo by conventional pen (NovoPen III; Novo Nordisk). On the other occasion, the order was reversed.

Analytical Procedures

Plasma glucose levels were determined in duplicate, immediately after blood sampling by the glucose oxidase method (Beckmann glucose analyzer II; Beckman Instruments, Fullerton, CA, USA). Blood sampled for plasma insulin measurements were centrifuged and stored at −20 °C for later measurement by radioimmunoassay [8].

Endpoints and Calculations

The pharmacodynamic and pharmacokinetic endpoints were derived from the glucose infusion rate (GIR) and the insulin concentration profile, respectively, and consisted of the time to maximal glucose infusion rate (T-GIR_{max}) and time to maximal insulin concentration (T-INS_{max}).

Statistical Analyses

All data are expressed as means with 95% confidence intervals (95% CIs), unless otherwise indicated. Mean outcomes were tested by paired *t*-tests. Pharmacologic data were analysed in subgroups defined by median BMI (highest vs. lowest 50%, n = 9 per subgroup) and by analysis of the correlations between BMI and absorption parameters both as continuous variables. Similar analyses were performed with waist circumference (WC), waist-to-hip ratio (WHR) and insulin dose. Correlations were calculated using the Pearson's correlation test. All statistical analyses were performed by SPSS 16.0 (Statistical Package for Social Sciences, Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

Five men and 13 women were included. Mean age was 27.2 years (range 19–49 years). The median body weight was 68.6 kg (50.5–93.9 kg), median insulin dose administered was 13.7 U (10.1–18.8 U), median BMI was 23.6 kg/m^2 (18.1–28.0 kg/m^2), median WC was 80 cm (65–98 cm) and median WHR was 0.79 (0.67–0.93).

Subgroup Analysis for Conventional Insulin Pen

When insulin was injected by conventional pen, T-INS_{max} was 31.1 (95% CI 13.7–48.5) min later and T-GIR_{max} 56.9 (26.6–87.3) min later in subjects with a BMI above the median than in subjects with a BMI below the median (figure 1). Similar results were obtained in subgroups defined by WC and WHR (data not shown). T-GIR_{max} was significantly correlated with BMI, WC, WHR and insulin dose, and T-INS_{max} was associated with BMI, WC and WHR (Table 1).

Subgroup Analysis for Jet Injector

When insulin was injected by the jet injector, neither T-INS_{max} nor T-GIR_{max} differed between subjects with indices of body composition or insulin dose above median values vs. below median values (figure 1). Both T-INS_{max} and T-GIR_{max} were unrelated to BMI, WC, WHR or the insulin dose (Table 1).

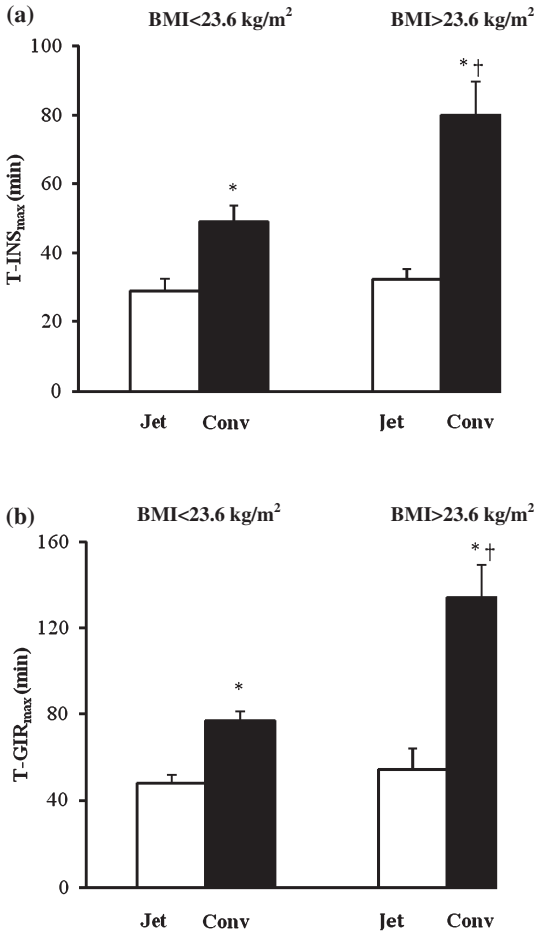

Figure 1. T-INS_{max} (a) and T-GIR_{max} (b) for the jet injector (Jet, white bar) and conventional pen (Conv, black bar) in subgroups of patients with a body mass index (BMI) below and above 23.6 kg/m^2 (nine participants in every subgroup). *$p < 0.05$ vs. jet injection in similar BMI subgroup; †$p < 0.05$ vs. BMI <23.6 kg/m^2 in same injection group.

The pharmacologic benefit of jet injection over conventional pen injection was proportionally larger in subjects with a high BMI than in those with a low BMI. Jet injection reduced T-INS_{max} by 20.0 (8.5–31.5) min in subjects with a BMI below the median and by 47.8 (26.5–69.1) min in subjects with a BMI above the median ($p = 0.018$). T-GIR_{max} was reduced by 29.2 (6.4–51.9) min and 79.7 (41.9–117.6) min in subjects with low BMI and high BMI, respectively ($p = 0.018$, figure 1). The bioavailability of insulin, as derived from the area under the insulin concentration curve, did not differ between the two devices in any of the subgroups. No hematomas or skin redness were seen after jet injection.

Discussion

In this *post hoc* analysis, we show that the pharmacology of rapid-acting insulin injected by jet injection is not affected by BMI, WHR and WC. However, in accordance with previous observations in subjects with overt obesity (BMI ≥ 30 kg/m^2) [1–3], high BMI, WHR and WC were

Table 1. Correlations between pharmacologic parameters and parameters of central obesity or insulin dose.

	Conventional pen		Jet injector	
	Correlation coefficient	p-value	Correlation coefficient	p-value
BMI				
T-GIR_{max}	0.556	0.017	0.137	0.592
T-INS_{max}	0.579	0.012	0.059	0.815
WHR				
T-GIR_{max}	0.496	0.037	0.063	0.805
T-INS_{max}	0.506	0.032	0.065	0.799
WC				
T-GIR_{max}	0.557	0.016	0.027	0.914
T-INS_{max}	0.563	0.015	−0.012	0.961
Insulin dose				
T-GIR_{max}	0.542	0.020	0.287	0.249
T-INS_{max}	0.419	0.083	0.014	0.954

WC, waist circumference; WHR, waist-to-hip ratio.

significantly associated with delays in absorption and onset of action when insulin was administered by conventional insulin pen.

A possible explanation for the dissociation of adiposity indices and insulin absorption or action when insulin was administered by jet injection is the spray-like dispersion pattern in the subcutaneous tissue, which facilitates distribution of insulin over a relatively large absorptive area and therefore allows for a more rapid absorption of insulin into the circulation [7]. Because tissue dispersion increases when larger insulin doses are injected, the rate of absorption is much less a function of the dose administered than it is with conventional pen [4].

A limitation of the present analysis is that it was not prespecified in the study protocol. However, our findings with regard to the conventional pen are in line with previous studies showing delayed insulin absorption in the obese [3]. Other limitations concern the rather narrow BMI range of our study population and the fact that patients with diabetes were not investigated. Appropriately designed studies are necessary to confirm these results in obese subjects, especially those with (type 2) diabetes and to determine whether the long-term effect of these favourable pharmacologic properties translate into better glycaemic control and lower risk of (late postprandial) hypoglycaemia.

In conclusion, this analysis shows that higher body weight indices or insulin dose do not modulate the pharmacological profile of subcutaneous insulin when administered by jet injection, whereas significant delays can be observed after insulin administration by conventional pen. As a result, the improvement in the pharmacologic profile of rapid-acting insulin injected by jet injection appears to be greater for patients with a higher BMI. This may be clinically relevant for patients with type 1 or type 2 diabetes who are overweight or obese.

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Conflict of Interest

EPG funded the study, but was not involved in the design or execution of the study or in the analyses of the data or writing of manuscripts. The authors have no other conflicts of interest to declare.

B. E. D. G. and C. J. T. designed the study. E. J. A. and B. E. D. G. wrote the study protocol. E. E. C. E., E. J. A. and B. E. D. G. performed the experiments and analyzed the data. B. E. D. G. drafted the first version of the manuscript. All authors interpreted the data, edited the paper and approved the final version of the paper.

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