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ORIGINAL ARTICLE

Insulin administered by needle-free jet injection corrects marked hyperglycaemia faster in overweight or obese patients with diabetes

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Aims: To test whether jet injection of insulin resulted in faster correction of marked hyperglycaemia than when insulin is injected by a conventional pen in patients with diabetes.

Methods: Adult, overweight or obese (BMI $\geq$25 and $\leq$40 kg/m^2) patients with type 1 diabetes (n = 10) or insulin-treated type 2 diabetes (n = 10) were enrolled in a randomized, controlled, crossover study. On two separate occasions, patients were instructed to reduce insulin dose(s) to achieve marked hyperglycaemia (18–23 mmol/l). Subsequently, insulin aspart was administered either by jet injection or by conventional pen, in a dose based on estimated individual insulin sensitivity. Pharmacodynamic and pharmacokinetic profiles were derived from plasma glucose and insulin levels, measured for 6 h after injection.

Results: After conventional injection, plasma glucose concentration dropped by $\geq$10 mmol/l after 192.5 $\pm$ 13.6 min. The jet injector advanced this time to 147.9 $\pm$ 14.4 min [difference 44.6 (95% confidence interval 4.3, 84.8); $P = 0.03$], except in 3 patients who failed to reach this endpoint. The time advantage exceeded 1.5 h in patients with a BMI above the median. Jet injection also reduced the hyperglycaemic burden during the first 2 h (2042 $\pm$ 37.2 vs 2168 $\pm$ 26.1 mmol/min; $P = 0.01$) and the time to peak insulin levels (40.5 $\pm$ 3.2 vs 76.8 $\pm$ 7.7 min; $P < 0.001$), but did not increase the risk for hypoglycaemia.

Conclusions: Administration of rapid-acting insulin by jet injection results in faster correction of marked hyperglycaemia in overweight or obese patients with insulin-requiring diabetes.

Keywords: clinical trial, insulin therapy, pharmacodynamics, pharmacokinetics, type 1 diabetes, type 2 diabetes, hyperglycaemia

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Introduction

Hyperglycaemia frequently occurs in patients with diabetes and significantly affects overall glycaemic control, even when elevated glucose levels exist only for a short period of time [1]. When considerable, hyperglycaemia may cause symptoms, e.g. thirst, dizziness or headache, and predispose to severe metabolic disturbances when not corrected quickly. The correction of marked hyperglycaemia is often difficult, because glucose toxicity resulting from hyperglycaemia may induce insulin resistance, leading to a higher insulin dose requirement. Moreover, high insulin doses are probably more slowly absorbed than smaller doses [2], which may prolong the time spent in hyperglycaemia and tempt the individual to repeat the insulin injection, resulting in an increased risk of late hypoglycaemia.

Insulin administration by jet injection is a needle-free alternative to conventional injections, which delivers insulin at high velocity (typically >100 m/s) across the skin, dispensing it over a larger subcutaneous area than insulin injected with a needle [3]. This method of insulin administration, first developed in the 1950s [4], significantly accelerates insulin absorption from the subcutaneous tissue into the systemic circulation, resulting in a more direct onset and shorter duration of insulin action as compared with insulin injected with a needle [3–10]. We recently compared the efficacy of a contemporary jet injector (Insujet™; European Pharma Group, Schiphol-Rijk, The Netherlands) with that of a frequently used conventional insulin pen for the administration of a rapid-acting insulin analogue. Both in healthy participants without diabetes and in patients with type 1 or insulin-treated type 2 diabetes, the jet injector considerably advanced insulin absorption and its subsequent glucose-lowering effect [11,12]. Furthermore, jet injection reduced the hyperglycaemic burden after a standardized meal [12].

The shorter time–action profile of insulin administered by jet injection may be especially advantageous for the correction of marked, potentially hazardous, hyperglycaemia. We therefore hypothesized that insulin administered by jet injection would result in more immediate and faster correction of marked hyperglycaemia than insulin administered by a conventional insulin pen. Because the rate of absorption of insulin injected by jet stream is much less affected by higher insulin doses and body weight than insulin injected conventionally [12,13], the aim of the present study was to test this hypothesis in patients

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with type 1 diabetes or insulin-treated type 2 diabetes who were either overweight or obese. We also aimed to compare the pharmacokinetics, safety and ease of use of both modes of insulin administration.

Materials and Methods

This randomized, controlled, crossover study was conducted at the Radboud university medical center between March and October 2014. The study was approved by the institutional review board of the Radboud and conducted according to Good Clinical Practice. All participants provided written informed consent and received a reimbursement. The trial was registered at ClinicalTrials.gov under the number: NCT01947556.

Participants

Potentially eligible subjects with type 1 or type 2 diabetes were selected from the Radboud university medical center outpatient diabetes clinic or recruited by social media. They were men or women aged 18–75 years, with a body mass index (BMI) of ≥25 and ≤40 kg/m^2 and glycated haemoglobin concentration (HbA1c) of ≥6.5 and ≤10% (≥48 and ≤86 mmol/mol), who were treated with basal-bolus insulin for at least 12 months, either by multiple daily injections with basal and prandial insulin or by subcutaneous insulin pump. Exclusion criteria were insulin requirement of <34 or >200 units per day (based on the minimum and maximum amount of insulin that could be injected by jet injection), use of oral antidiabetic agents or drugs known to interfere with glucose control other than metformin (a 4-week wash-out of thiazolidinediones, sulphonylurea and dipeptidyl peptidase-4 inhibitors was allowed), known allergy to aspart insulin, symptomatic diabetic neuropathy, history of a major cardiovascular event in the previous 6 months, liver enzymes ≥3.0 times the upper limit of normal, plasma creatinine >150 µmol/l, anaemia (haemoglobin <7.5 or <8.3 mmol/l for females and males, respectively) and pregnancy.

Randomization and Study Procedures

The participants who were enrolled underwent two separate test days. Experiments started at 07:30 hours, with the patient in fasting condition, and having abstained from smoking, alcohol use and caffeine-containing substances for 24 h before the experiments. On the day before the experiments, patients were instructed to interrupt or reduce the use of long-acting insulin and short-acting prandial insulin in order to reach hyperglycaemia, targeting next-morning plasma glucose values of 15–18 mmol/l. Patients with insulin pumps were instructed to reduce the basal rate the evening and night before the experiment, and to stop the pump 2 h before the experiment. Reductions in insulin dose were determined on an individual basis, and instructions were given to inject short-acting insulin according to an individualized schedule if glucose levels exceeded 18–20 mmol/l up to 2 h before arrival at the research unit.

The experiments were performed with the patient in a supine position in a temperature-controlled room (22–24 °C). First, a catheter was inserted in retrograde fashion in a dorsal hand vein for frequent blood sampling, whereby the hand was placed inside a heated box (~55 °C) to arterialize venous blood [14]. Next, plasma glucose was measured to determine whether the glucose level was in the target range of 18–23 mmol/l. In case the glucose value was too low, we either (i) awaited the spontaneous rise in plasma glucose for a maximum of 3 h; (ii) administered soda drink and subsequently waited for a minimum of 45 min until glucose levels had stabilized in the target range; or (iii) postponed the experiment if we expected that the glucose target was unattainable within 3 h.

After a stable plasma glucose level in the target range was obtained (as determined by 2–3 glucose values measured within a 15-min interval with a <2 mmol/l difference), the required insulin dose was calculated as the number of units required to reduce the plasma glucose value to 6 mmol/l, using the following formula:

$$\text{insulin dose} = \left(\left[\text{glucose} - 6\right] \div \left[\text{insulin sensitivity factor}\right]\right) \times 1.5,$$

where glucose is the measured glucose value in mmol/l. The insulin sensitivity factor reflects the expected fall in plasma glucose after administration of 1 unit of insulin, and is calculated by dividing 100 by the total daily insulin dose [15]. We used a multiplicity factor of 1.5 to ensure that sufficient insulin was administered to overcome hyperglycaemia-induced glucose toxicity and rounded the outcome up to the nearest round number or to a maximum of 40 units, as this was the maximum single dose the jet injector could inject. The calculated dose of aspart (Novorapid; Novo Nordisk, Bagsvaerd, Denmark) was administered subcutaneously in the abdomen either by jet injection (Insujet) or by conventional insulin pen (Flexpen®; Novo Nordisk). The Insujet jet injector delivers insulin across the skin with a short 'click' of 50–60 dB. The sequence by which the two devices were tested was randomized (1 : 1) by blocks of two according to diabetes type, using a computer-generated random number list. All participants were trained to use both devices. When possible (with the dominant hand free from cannulation), the injection was given by the participant under supervision of the research staff, as previously described [11].

After insulin administration, plasma glucose was measured on site using the glucose enzymatic-amperometric method (Biosen C-line GP+; EKF-diagnostic GmbH, Barleben, Germany), at 5-min intervals for the first 3 h, and at 10-min intervals for the subsequent 3 h. Also, blood was drawn, processed, and serum was stored at −80 °C for later determination of plasma insulin levels by radioimmunoassay every 10 min during the first hour, every 15 min during the second hour, and every 30 min thereafter [16].

When glucose values dropped below 4.8 mmol/l, glucose 20% was infused intravenously through another catheter that was placed as needed, to prevent hypoglycaemia. Within 30 min after insulin injection, a questionnaire was administered, asking participants to point out, on a numeric rating scale from 0 to 10, the amount of discomfort or pain and the ease of use experienced with the tested administration method, and the device they would prefer for insulin injection should they have a choice. The experiments were terminated 6 h after the insulin injection, and the patients were given a meal. The second

experimental day was scheduled 2–4 weeks later, following the same procedure and testing the other device.

Outcome Measures

The primary endpoint was the time needed to achieve a drop in plasma glucose concentration of ≥10 mmol/l ($T\text{-}BG_{\geq 10}$). Secondary pharmacodynamic endpoints included the time in min until plasma glucose values had dropped below 10 mmol/l ($T\text{-}BG_{10}$) and 5 mmol/l ($T\text{-}BG_{5}$); the slope of the glucose fall (R_{fall}), calculated from the time–glucose curve; and the hyperglycaemic burden for the first 2 h ($BG\text{-}AUC_{0-2h}$) and total 6 h ($BG\text{-}AUC_{0-6h}$) post-injection, reflected by the areas under the 2- and 6-h time–glucose curves, respectively. Secondary pharmacokinetic endpoints were the time to maximum insulin concentration ($T\text{-}INS_{max}$); maximum insulin concentration ($C\text{-}INS_{max}$); the area under the baseline-corrected insulin-concentration curve (INS_{AUC}), reflecting total insulin absorption; and the time until 50% of insulin absorption ($T\text{-}INS_{AUC50\%}$). Tolerability was tested by the amount of discomfort or pain and the ease of use experienced with the two administration methods using a numeric rating scale, and the proportion of subjects preferring the jet injector for insulin administration. Safety was tested by the number of patients requiring exogenous glucose infusion to prevent hypoglycaemia (blood glucose ≤4.8 mmol/l) after insulin injection, the amount of exogenous glucose required, and the duration of glucose administration.

Statistical Analysis

As we previously found a 29.2 ± 42.1 min (~25%) reduction in time to achieve a similar glucose-lowering effect over the first 2 h after administration of a standard insulin dose by jet rather than conventional injection [11], we calculated that 17 participants would be required to detect a ~30-min reduction in time to achieve the primary endpoint with 80% statistical power at a 5% level of significance. To correct for the relatively small number of subjects involved, a total of 20 subjects were enrolled, and additional participants were recruited in case of drop-out. To perform subgroup analyses, we enrolled an equal number of patients with type 1 and type 2 diabetes. All data are expressed as mean ± standard error (s.e.); differences are expressed as means with 95% confidence intervals (CIs), unless otherwise indicated.

Paired *t*-tests (or Wilcoxon signed-rank tests for non-parametric data) were performed to compare most study endpoints; in case of missing data for one of the pairs, e.g. when an endpoint was not reached, we performed unpaired *t*-tests (or Mann–Whitney *U*-tests). Glucose and insulin values for the two devices were analysed with two-way repeated measures ANOVA. The chi-squared test or Fisher's exact test was used as appropriate for analysis of differences in categorical variables. Subgroup analyses were performed using a linear mixed model, with fixed effects for device-by-subgroup interaction. Data were entered in a validated data management system (MACRO; InferMed Ltd, London, UK), and analysed according to intention to treat, using SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, NY, USA). *P* values <0.05 were considered to indicate statistical significance.

Table 1. Baseline characteristics.

	Type 1 diabetes (n = 10)	Type 2 diabetes (n = 10)
Sex, male : female	7 : 3	7 : 3
Mean ± s.d. age, years	48 ± 12	59 ± 7
Mean ± s.d. diabetes duration, years	28.7 ± 11.9	17.8 ± 8.2
Median (range) insulin treatment duration, years	28.9 (8.5–45.3)	10.9 (7.2–19.6)
Mean ± s.d. body weight, kg	93.8 ± 12.0	106.2 ± 15.8
Mean ± s.d. BMI, kg/m^2	29.7 ± 3.7	34.7 ± 4.3
Mean ± s.d. waist circumference, cm	99.7 ± 5.5	111.1 ± 17.1
Mean ± s.d. HbA1c, % (mmol/mol)	8.4 ± 1.1 (68 ± 12)	8.7 ± 1.1 (72 ± 12)
Median (range) insulin dose, Units/day	57 (34–109)	136 (36–200)
Insulin regimen, n		
Basal-bolus	4	8
Pump therapy	6	2
Oral glucose-lowering medication, n		
Metformin only	1	3
Metformin and DPP-4 inhibitor	0	1
Thiazolidinedione	0	1
Current smoker, n	0	2

DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; s.d., standard deviation.

Results

A total of 26 patients with diabetes were screened, 23 of whom were included. Two were not eligible because they did not meet HbA1c criteria, and 1 was excluded because of anaemia. After inclusion, three subjects were excluded and subsequently replaced: 1 participant did not reach hyperglycaemia after interrupting insulin administration for 72 h, and 2 participants withdrew consent after the first experimental day was postponed, because of not reaching the hyperglycaemic target. The baseline characteristics of all subjects who underwent testing are shown in Table 1. In three cases, the experiment was rescheduled: in 1 patient, the insulin dose was erroneously calculated too low, and in two cases the jet injector produced a 'wet injection', i.e. insulin was released before the injector made proper contact with the skin. Two additional experiments were postponed because the first measured plasma glucose value was <10 mmol/l. In 13 experiments (7 with a jet injector and 6 with the conventional pen; 10 among 6 patients with type 2 diabetes and 3 among 2 patients with type 1 diabetes), participants were given soda drink in order to reach the hyperglycaemic target. In half of the experiments, the patient operated the jet injector.

Mean (± SD) glucose values before insulin injection were 20.6 ± 2.5 and 21.3 ± 2.8 mmol/l for patients with type 1 and type 2 diabetes, respectively. These data were used to calculate the required insulin doses at 14.3 ± 5.9 and 29.1 ± 11.5 units. As the glucose values at baseline (at the moment of insulin

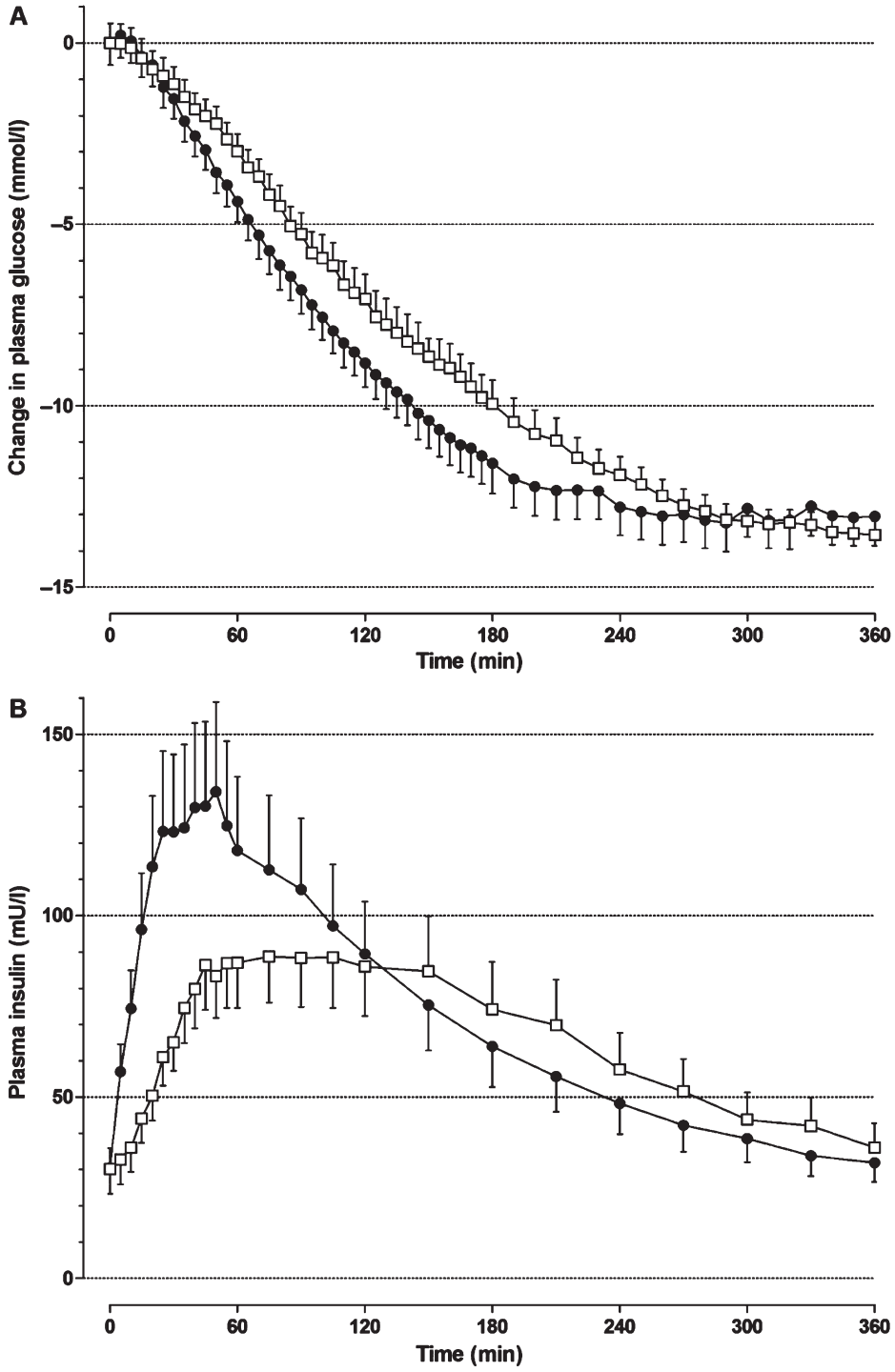

Figure 1. Changes in plasma glucose and insulin levels during the experiments. Mean ± standard error changes in plasma glucose levels (A) and plasma insulin levels (B) during the experiments, from baseline (moment of insulin administration) to 6 h after insulin administration by jet injection (black circles) and conventional insulin pen (white squares).

injection) differed slightly, but significantly, between the jet injector and conventional pen (22.2 ± 0.6 vs. 20.4 ± 0.5 mmol/l; p = 0.004), we used the change in glucose levels rather than absolute values for analyses concerning the area under the glucose curve and time to reach glucose values below 10 and 5 mmol/l.

Pharmacodynamic Endpoints

The fall in plasma glucose values during the experiments is shown in Figure 1A, the slope of which was significantly steeper with the jet injector than with the conventional pen (Table 2). The time until plasma glucose concentration had dropped

Table 2. Pharmacodynamic and pharmacokinetic endpoints.

Endpoint	Jet injector	Conventional pen	p
Pharmacodynamic endpoints			
T-$BG_{\geq 10}$, min	147.9 ± 14.4 (n = 17)	192.5 ± 13.6 (n = 20)	0.03
T-BG_{10}, min	163.2 ± 17.3 (n = 14)	214.1 ± 16.0 (n = 17)	0.04
T-BG_{5}, min	220.8 ± 21.5 (n = 6)	270.0 ± 17.3 (n = 3)	0.19
BG-$AUC_{0–2h,}$ mmol/min/l	2042 ± 37.2	2168 ± 26.1	0.01
BG-$AUC_{0–6h,}$ mmol/min/l	4226 ± 241.8	4539 ± 142.4	0.24
R_{fall}, mmol/l/min	0.080 ± 0.005	0.064 ± 0.004	0.03
Pharmacokinetic endpoints			
C-INS_{max}, mU/l	140.6 ± 24.4	101.7 ± 14.7	0.003
T-INS_{max}, min	40.5 ± 3.2	76.8 ± 7.7	<0.001
$INS_{AUC,}$ mU/min/l	14 363 ± 2498	12 390 ± 1858	0.06
T-$INS_{AUC50\%}$, min	107.1 ± 9.4	139.7 ± 5.9	0.003

n represents the number of patients that reached the endpoint. BG-$AUC_{0–2h\ (0–6h)}$, area under the time–glucose curve, reflecting post-injection hyperglycaemic burden, from 0 to 2 (6) h after insulin injection; C-INS_{max}, maximum insulin concentration; INS_{AUC}, area under the insulin concentration curve, reflecting total insulin absorption; R_{fall}, slope of the glucose fall, calculated from the time–glucose curve during the first 30–120 min of the test; T-$BG_{\geq 10}$, time until plasma glucose concentration had dropped by ≥10 mmol/l; T-$BG_{5\ (10)}$, time until plasma glucose values had dropped below 5 (10) mmol/l; T-$INS_{AUC50\%}$, time until 50% of insulin absorption; T-INS_{max}, time in min to maximum insulin concentration.

≥10 mmol/l was 147.9 ± 14.4 min after insulin administration by jet injection, compared with 192.5 ± 13.6 min after insulin administration with a conventional pen [difference 44.6 min (95% CI 4.3–84.8); $P = 0.03$]. In 2 patients with type 1 and 1 patient with type 2 diabetes (mean BMI 32.6 ± 2.8 kg/m^2), the primary endpoint was not reached on the jet injection day. The maximum falls in plasma glucose were 4.8, 8.6 and 9.6 mmol/l, with corresponding peak insulin levels of 63.1, 66.0 and 118.6 mU/l, respectively. Recalculation of the data (using a paired *t*-test) after exclusion of these patients did not materially change the outcome (147.9 ± 14.4 vs 197.9 ± 15.0 min for jet injector and conventional pen, respectively; p = 0.012). Similarly, when we calculated the time until all patients achieved the minimum measured fall in plasma glucose of 4.8 mmol/l, the jet injector still performed significantly faster than the conventional pen (80.8 ± 14.4 vs 92.5 ± 4.8 min; p = 0.007).

After 1 h, glucose values had dropped by 4.4 ± 0.3 mmol/l after jet injection and by 3.0 ± 0.2 mmol/l after conventional injection (p = 0.001). The hyperglycaemic burden, as reflected by the area under the glucose concentration curve was significantly less for the jet injector during the first 2 h after insulin administration (p = 0.01; Figure 1A and Table 2), but did not differ for the remainder of the test. The times until plasma glucose values dropped below 10 and 5 mmol/l were also numerically shorter for the jet injector than for the conventional pen, but not statistically as these endpoints were achieved in a subset of patients (Table 2).

In subgroup analyses, a higher BMI was independently associated with a greater time benefit of jet injection with respect to the primary endpoint (97.2 ± 19.2 vs. 3.1 ± 17.0 min for BMI above and below the median of 31.2 kg/m^2, respectively; p = 0.007), but diabetes type was not (p = 0.31). The use of soda drink before the experiments had no effect on this outcome (time benefit of jet injection 57.5 ± 31.9 min for soda-users compared with 43.3 ± 19.5 min for non-users; p = 0.703), or on any of the other outcomes.

Pharmacokinetic Endpoints

Insulin values could be measured in all patients except for 1, in whom the presence of insulin antibodies resulted in cross-reactivity with the analysis. The changes from baseline in plasma insulin levels for both devices are shown in Figure 1B. Jet injection advanced the absorption of insulin compared with conventional injection, as reflected by a shorter time to peak insulin levels (40.5 ± 3.2 vs 76.8 ± 7.7 min; p < 0.001; Table 2) and ~50% higher peak insulin levels (140.6 ± 24.4 vs 101.7 ± 14.7 mU/l; p = 0.003). Jet injection significantly advanced the time in minutes until 50% of insulin absorption (by 32.6 min; $P = 0.003$). Total insulin absorption, reflected by the area under the insulin-concentration curve, appeared to be greater after jet than after conventional injection [difference 1973 mU/min/l (95% CI −229.2 to 4175.2), $P = 0.06$; Table 2], yet this was probably the consequence of the slightly greater insulin dose injected by jet stream. In 1 of the 3 patients who did not reach the primary pharmacodynamic endpoint, insulin levels remained relatively low (INS_{AUC} 958.1 mU/min/l; maximum drop in plasma glucose 4.8 mmol/l), suggesting insufficient insulin administration or absorption, whereas insulin levels were appropriately elevated in the other two cases (7049 and 8448 mU/min/l; maximum drop in plasma glucose 9.6 and 8.6 mmol/l).

Safety and Ease of Use

In seven experiments (18%), three with the jet injector and four with the conventional pen, all in patients with type 1 diabetes, exogenous glucose was administered to prevent hypoglycaemia. There were no differences between the two devices in the time to the start of glucose administration (208 ± 8 vs 218 ± 40 min; p = 0.84), or the amount of exogenous glucose administered (14.3 ± 5.3 vs 17.7 ± 8.2 g; p = 0.77). Adverse effects reported during the experiments were mostly mild to moderate in nature, and associated with hyperglycaemia (thirst, polyuria and nausea), which resolved quickly after glucose levels decreased. One patient requiring glucose infusion developed

phlebitis, which resolved without treatment within 4 weeks. The amount of pain or discomfort experienced with the jet injector or conventional pen was rated 1.8 ± 0.4 and 1.2 ± 0.1 (p = 0.38), respectively; the (un)ease of use was rated 2.7 ± 0.4 with jet and 1.6 ± 0.2 with conventional pen injection (p = 0.49). Of the 20 patients included, 6 preferred the jet injector, 7 preferred the conventional pen, and 7 did not have a preference (p = 0.95).

Discussion

The present study shows in overweight or obese patients with type 1 or type 2 diabetes that administration of a rapid-acting insulin analogue by jet injection resulted in faster correction of hyperglycaemia, by ~45 min, compared with administration with a conventional insulin pen. Insulin administration by jet injection also decreased the hyperglycaemic burden during the first 2 h, without posing a greater risk of late hypoglycaemia. The two devices were rated equally, both with respect to discomfort as with respect to ease of use by the trial population, consisting of diabetes patients highly experienced with and unbiased towards contemporary insulin therapy. These findings suggest that insulin administration by jet injection provides an effective and user-friendly way to correct marked hyperglycaemia in patients with insulin-treated diabetes.

The advantage of insulin administration by jet over that by conventional injection with respect to normalizing plasma glucose levels, duration of hyperinsulinaemia, and hyperglycaemic burden, is in line with our previous studies conducted both in healthy subjects and in subjects with diabetes [11–13], and with studies comparing jet injectors with needle syringes [3,5–9]. Indeed, in those studies, jet injection reduced both the time to peak insulin levels and to maximum insulin action as well as the duration of insulin action by ~30–45 min. Also in line with previous results is our observation that jet injection appeared most beneficial for patients with higher BMI, who consequently required more insulin, although the underlying mechanism remains to be explained [13].

Most guidelines recommend to measure plasma glucose 1 h after administration of a corrective insulin dose for (marked) hyperglycaemia [17]; however, the initial drop in plasma glucose concentration after conventional pen injection in the present study was only 3 mmol/l (range 1.1–4.6 mmol/l). A glycaemic response that is too small may tempt patients and healthcare providers to repeat the insulin injection, which in turn increases the risk of late hypoglycaemia. Administration by the jet injector resulted in an almost 50% greater glucose fall. Other benefits of advanced correction of marked hyperglycaemia include less time spent in hyperglycaemia and the resultant potential to avert metabolic complications such as diabetic ketoacidosis and hyperosmolar hyperglycaemic state, potentially fatal conditions that often necessitate hospital admission [1,18]. Finally, apart from its use in an outpatient setting, the jet injector may also prove useful in the hospital, where hyperglycaemia is frequently encountered and difficult to manage [17].

In the present trial, we used an adjusted formula based on the individual insulin sensitivity factor to calculate insulin doses adjusted to individual patient needs. This contrasts with the more or less fixed sliding-scale algorithms used in daily practice and in most other trials conducted in patients with diabetes experiencing hyperglycaemia [14,19,20]. This easy-to-use calculation turned out to perform well, leading to adequate correction of marked hyperglycaemia in 93% of cases.

The present study has strengths and weaknesses. A strength of our trial is that it reflects real-world practice, in that hyperglycaemia was reached without parenteral interventions, much the same as in daily life. A weakness of the study is inherent to its design, in that it allowed glucose values to differ slightly between the two test days. However, the difference in baseline glucose values was small (<10% from the mean value) and unlikely to have had a meaningful impact on any of the outcomes. To further represent real-world practice, the device was operated by the patient when feasible. Although the lack of a double-blind design may be criticized, it is hard to imagine how this would change the results, as the insulin-induced fall in glucose is difficult to manipulate. We made sure that all conditions were exactly the same on both testing days, so that any potential modulation by the participant or research staff was kept to an absolute minimum. The absence of a placebo injection might therefore only have had minimal, if any, influence on the results.

In 2 participants, insulin administration by the jet injector resulted in a 'wet-injection', for which we had to reschedule the test day. In another participant, even though we did not observe a wet injection, hyperglycaemia was inadequately corrected because of low plasma insulin levels, suggesting insufficient insulin absorption from the subcutaneous tissue. Such errors are obviously undesirable for a product that needs to be administrated on a daily basis [21], and underscore that handling this device may be cumbersome. Previous research showed that administration of an entire insulin dose by jet injection can be achieved in almost all circumstances, when sufficient training is provided [22]. Nevertheless, the interindividual variability in insulin action observed in the present study appeared not to differ between conventional and jet injection. In line with our previous research, insulin administration by this jet injector was well tolerated and not dissimilar from conventional pens [12]. Finally, it should be acknowledged that the pharmacological profile of insulin injected by jet stream and the tolerability of the device are specific to the jet injector used in the present study; our data cannot simply be extrapolated to other jet injectors [23].

In conclusion, aspart insulin administered by jet injection results in a more rapid and equally safe correction of marked incidental hyperglycaemia as compared with administration by a conventional insulin pen, especially in patients with a higher BMI. These effects may be clinically relevant for patients with diabetes treated with rapid-acting insulin. Further research is needed to elucidate the applicability of jet injection in daily practice.

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Conflict of Interest

B. E. d. G. served as a consultant for, or gave lectures organized by Novo Nordisk, Merck and Sanofi. C. J. T. has received research grants, served as a consultant for, or gave lectures organized by Merck, Janssen, AstraZeneca and Novo Nordisk. The remaining authors declare that they have no conflicts of interest.

H. M. d. W. designed the study, performed the experiments, analysed and interpreted the data, drafted and revised the manuscript, and approved the final version of the manuscript. E. E. C. E. performed the experiments, analysed and interpreted the data, revised the manuscript, and approved the final version of the manuscript. C. J. T. designed the study, interpreted the data, revised the manuscript and approved the final version of the manuscript. B. E. d. G. designed the study, performed the experiments, analysed and interpreted the data, revised the manuscript, approved the final version of the manuscript and obtained funding.

B. E. d. G. 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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