Journal of Diabetes Science and Technology
Volume 5, Issue 5, September 2011

ORIGINAL ARTICLE

Injection Force of Reusable Insulin Pens: Novopen 4, Lilly Luxura, Berlipen, and ClikSTAR

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Abstract

Background:

Insulin pen devices are used by approximately half of insulin users worldwide. The injection force of insulin pens is a key element in their design. This study aimed to demonstrate that the sanofi-aventis reusable ClikSTAR® (CS) pen has an improved injection force over existing insulin pens.

Methods:

The injection force of four reusable insulin pens—Novopen® 4 (NP4; Novo Nordisk), Luxura® (LL; Eli Lilly and Co.), Berlipen® (BP; Haselmeier GmbH), and CS (sanofi-aventis)—was tested in a laboratory setting. Injection force was tested using two methods: six dispense rates between 6 and 24.66 U/s (constant volume flow rate) and constant button speeds of 4 and 8 mm/s.

Results:

The CS required a lower mean injection force versus NP4, LL, and BP at both doses and all dispense rates. Mean injection force was 45%, 126%, and 60% higher for NP4, LL, and BP versus CS, respectively ($p < .05$ for each of the comparisons), for a flow rate of 6 U/s at 60 U dose. Mean injection force in all pens increased with the dispense rate, but the injection force remained significantly lower for CS versus all other pens ($p < .05$). The injection force for CS was significantly lower for 60 U at 10 and 17.03 U/s than for 80 U.

Conclusions:

The study demonstrated that CS pens require a lower injection force at a wide range of different injection speeds than other reusable insulin pens. This is an important benefit for patients with diabetes, especially those with limited dexterity.

J Diabetes Sci Technol 2011;5(5):1185-1190

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Abbreviations: (BP) Berlipen, (CS) ClikSTAR, (LL) Luxura, (NP4) Novopen 4

Keywords: Berlipen, ClikSTAR, injection force, insulin pens, Lilly Luxura, Novopen 4

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Introduction

Since their introduction in the 1980s, use of insulin pens has revolutionized the treatment of type 1 and type 2 diabetes. Insulin pen devices are currently being used by over 60% of insulin users worldwide and are associated with lower annual treatment costs.[1–3] Insulin pens are known to be preferred by patients, easy to use, discreet, and associated with improved patient compliance.[2–9] The evolution of insulin pens has been associated with improvements in dosing accuracy and shorter injection times.[10–13]

The injection force of insulin pens is one of the key elements in their design, along with dose accuracy, maximum dose per injection, and ease of use.[1,14] Lower injection force has been associated with less injection-site pain,[15] simpler operation, and more comfortable use[16] and may be important to patients with diabetes. It is known that diabetes can lead to reduced finger joint mobility and lower hand strength, impaired muscle function, and carpal tunnel syndrome.[17–20] Use of easily operated insulin pen devices requiring less injection force would appear to be beneficial in such patients.

ClikSTAR® (CS; sanofi-aventis, Deutschland GmbH, Frankfurt am Main, Germany) is a reusable pen device for administration of insulins recommended by the pen manufacturer. In a user study, patients with type 1 or type 2 diabetes rated CS to be significantly easier to use than NovoPen® 4 (NP4; Novo Nordisk, Bagsvaerd, Denmark) and Luxura® (LL; Eli Lilly, Indianapolis, IN) and rated the overall performance of CS equal to or better than those pens.[21] The patient preference in that study was determined from questionnaires relating to the ease of use of the devices.

To further evaluate the CS pen, it is necessary to compare its injection force with that of other pens. Previous studies comparing insulin pens have been inconsistent in terms of methodology, including choice of flow rate[7] and constant button speed,[11,22] making direct comparison of injection forces between studies difficult. Distinctions between injection force findings may arise from differences in flow characteristics and stroke length.

The injection force of CS was evaluated in comparison with three other similarly designed (using manual thumb force for injection instead of automatic injection using a spring-loaded force for injection such as the Autopen®[23]) commercially available devices in a laboratory setting at both constant flow rates and constant button speeds. The study was also intended to determine the dependency of injection force on button speed and volume flow rate.

Methods

Study Design

The injection force of four reusable insulin pens, CS, NP4, LL, and Berlipen® (BP; Berlin-Chemie AG, Berlin, Germany), was evaluated in a laboratory setting (**Figure 1**) in which human subjects were not involved. Preliminary studies were conducted to determine button speeds for specific volume flow rates, and calculated regression lines were used to measure injection forces of the test pens at constant volume flow rates instead of constant

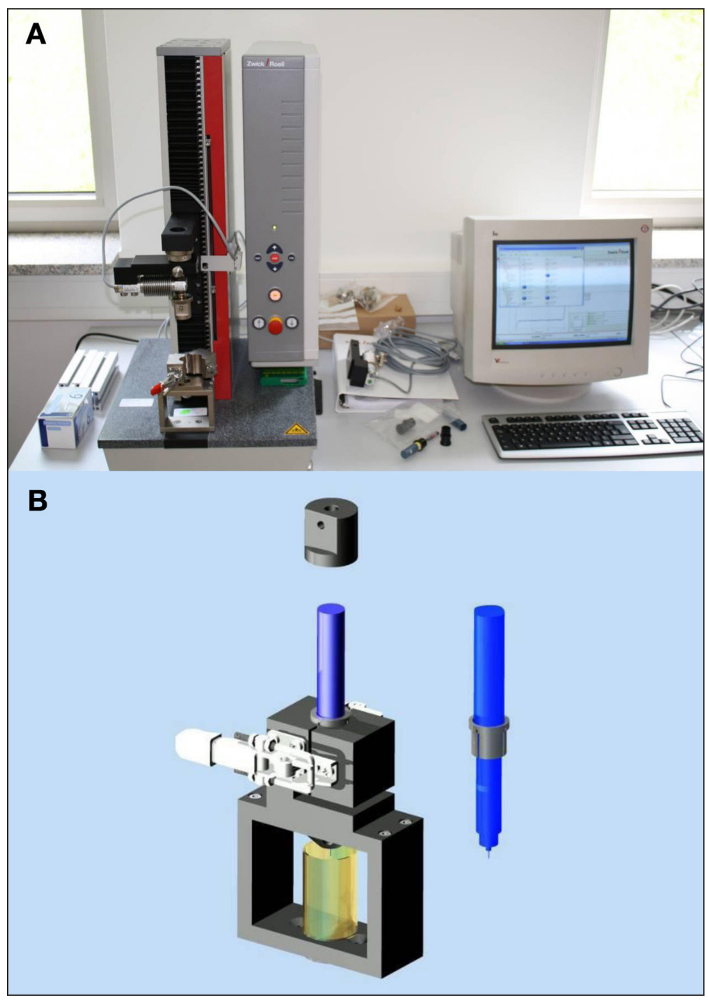

Figure 1. (A) The Zwicki Z0.5 TS and **(B)** the customized clamping tool.

button speeds as in other studies.[11,22] Injection force was validated by varying button speed and volume flow rate. Pens were tested at constant button speeds of 1, 4, and 8 mm/s and at constant flow rates of 6, 8.51, 10.0, 11.40, 17.03, and 23.66 U/s, with the exception of LL and BP, which were not tested at 11.40 and 23.66 U/s. Maximum doses were tested for all pens, which was 60 U for all pens except CS, for which the maximum dose was 80 U (**Table 1**). The CS was also tested at a dose of 60 U to enable direct comparison with the other pens.

Mean delivered doses, mean injection time, and mean injection force data were collected during this laboratory study.

Twenty pens of each type were fitted with needles recommended by the pen manufacturer (**Table 1**): Novofine (Novo Nordisk, Bagsvaerd, Denmark) for the NP4 and Becton Dickinson Microfine 31 G × 5 mm needles (Becton Dickinson, Franklin Lakes, NJ) for CS and LL. The recommended needle for the BP was the Becton Dickinson Microfine 30 G × 8 mm. This was used in the pretest, but for the main test, the Becton Dickinson Microfine 31 G × 5 mm needle was substituted. The insulin employed was that recommended by the pen manufacturer. This decision was made based on the approved use of each insulin pen and the fact that specific insulin cartridges only fit into the recommended pen device.

Three repetitions were performed for each pen at each button speed and at each flow rate. Injection force was measured using an isometric injection with a Zwicki Z0.5 TS tensile testing machine, which had been calibrated by the manufacturers prior to the tests. Dispensed insulin was measured using an OHaus Discovery DV 215 CD precision and analytical balance (capacity 210 g, repeatability 0.1 mg, linearity ± 0.2 mg).

Table 1.
Pen, Dosage, and Needle Combinations Tested

	Dosage		Needle		
	60 U	80 U	Becton Dickinson Microfine 31 G x 5 mm	Novo Nordisk Novofine 31 G x 6 mm	Berlin Chemie Berlifine 30 G x 8 mm
CS	✓	✓	✓	×	×
NP4	✓	×	×	✓	×
LL	✓	×	✓	×	×
BP	✓	×	✓	×	✓[a]

[a] Pretest only.

Measurement accuracy was verified and confirmed by means of reference weights.

Mean injection force was measured by dispensing the maximum dose of insulin (60 U for NP4, LL, and BP and 80 U for CS). Additional tests were conducted with CS at 60 U to allow a direct comparison with NP4, LL, and BP. Pens were tested with the insulin recommended by the pen manufacturer: glargine for CS, aspart for NP4, and isophane for LL and BP.

Statistical Analyses

An analysis of variance was used to compare the sample mean injection forces. Significance level was set to 5% (p = .05). Regression lines were generated for injection force at constant button speed and constant volume flow rate. Regression lines were determined for dispensed insulin calculated from dispensed volume (U) and injection time (s), and a linear regression algorithm was used to fit the injection speed as a function of dispensed insulin over time. Confidence intervals were used to determine significant difference for mean injection forces.

Results

Mean injection force data for pens tested are presented in **Table 2**. Injection force was 92%, 88%, and 28% higher with NP4, LL, and BP versus CS, respectively ($p < .05$), for a 60 U dose at a constant button speed of 4 mm/s (**Table 2**, **Figure 2**). Injection force was 45%, 126%, and 60% higher with NP4, LL, and BP versus CS, respectively ($p < .05$), for a 60 U dose at a constant flow rate of 6 U/s (**Table 2**, **Figure 3**).

All pens showed approximately linear increases in injection force with increase in flow rate, but injection force remained significantly lower for CS versus other pens ($p < .05$;

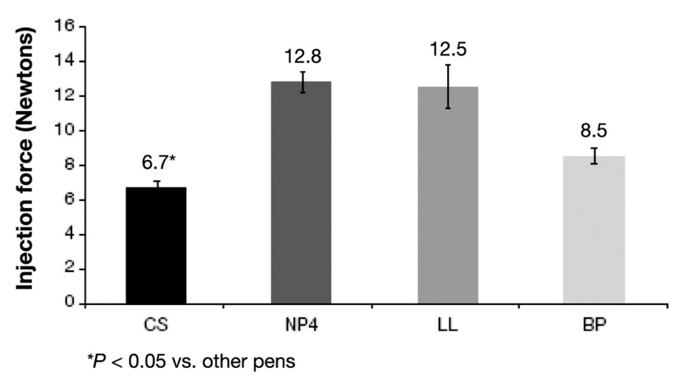

Figure 2. Mean (± standard deviation) injection force of reusable insulin pens at constant button speed (force required to inject 60 U at 4 mm/s).

Table 2.
Injection Forces (Observed Means ± Standard Deviation) by Pen

	CS		NP4	LL	BP
Dose	60 U *n* = 20	80 U *n* = 20	60 U *n* = 20	60 U *n* = 20	60 U *n* = 20
Constant button speed (values are given in mm/s)					
4	6.68 ± 0.44[a]	6.89 ± 0.42[a]	12.81 ± 0.58	12.54 ± 1.26	8.52 ± 0.44
8	14.11 ± 0.78[a]	14.78 ± 0.84[a]	26.41 ± 0.96	23.89 ± 2.19	16.36 ± 0.97
Constant flow rate (values are given in U/s)					
6	4.71 ± 0.35[b]	5.06 ± 0.40[b]	6.85 ± 0.28	10.63 ± 0.82	7.52 ± 0.82
8.51	6.68 ± 0.44	6.89 ± 0.42	9.19 ± 0.37	14.59 ± 1.07	10.34 ± 1.22
10	7.81 ± 0.57[b,c]	8.63 ± 0.69[b,c]	10.54 ± 0.38	16.61 ± 1.28	10.98 ± 1.19
11.4	9.22 ± 0.57	9.77 ± 0.49	12.81 ± 0.58	Not tested	Not tested
17.03	14.11 ± 0.78[b,c]	14.78 ± 0.84[b,c]	19.17 ± 0.92	25.72 ± 2.28	19.88 ± 1.12
23.66	20.56 ± 1.29	22.64 ± 1.65	26.41 ± 0.96[d]	Not tested	Not tested

[a] $p < .05$ compared with other pens at same button speed.
[b] $p < .05$ compared with other pens at same flow rate.
[c] $p < .05$ compared with NP4, LL, and BP at same flow rate.
[d] $n = 9$.

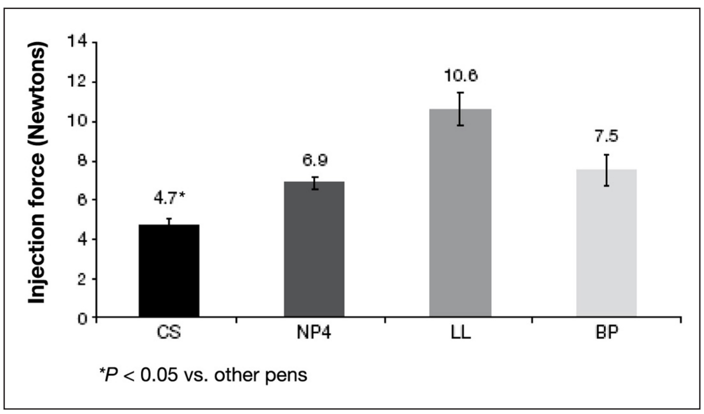

Figure 3. Mean (± standard deviation) injection force of reusable insulin pens at constant flow rate (force required to inject 60 U at 6 U/s).

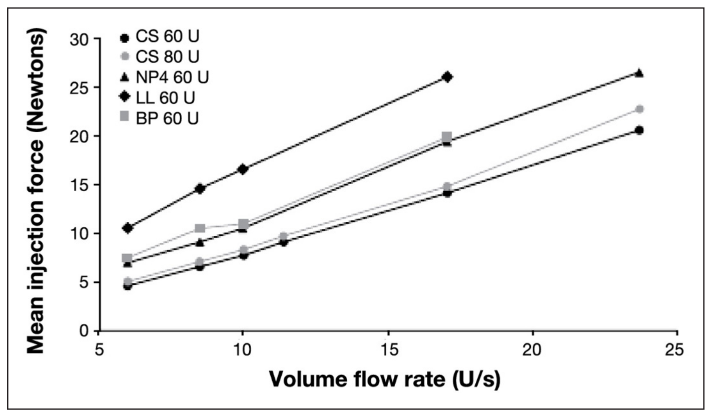

Figure 4. Mean injection force at different flow rates.

Table 2, **Figure 4**). Injection force for CS was significantly lower for 60 U than for 80 U at constant flow rates of 10 and 17.03 U/s (**Table 2**).

At constant dose button speeds of 4 and 8 mm/s and constant injection speeds of 6.00 and 8.51 U/s, mean injection forces of CS 80 and CS 60 were not significantly different (**Table 2**).

Discussion

Patient acceptance of insulin pens has been evaluated in clinical studies. In a comparison of NP4 with the reusable OptiClik pen (sanofi-aventis), patients were found to prefer NP4 over OptiClik in all areas of safety, size of pen, appearance, and ease of use.[24] The CS pen is a newer version of a reusable insulin pen designed to overcome the limitations of the OptiClik pen, and patients have subsequently shown a preference for CS compared with NP4 and LL.[21] However, few studies have considered the injection force of insulin pens. This study aimed to evaluate the injection force of CS in comparison with other commonly used reusable insulin pens.

Although the maximum dose of insulin is typically 60 U in Europe for patients with type 2 diabetes, doses up to 80 U and beyond are often used for obese patients in the United States who are taking basal insulin.

The performance of all pens was investigated at their current maximum doses (60 U for all pens tested except CS, which has been designed for a maximum dose of 80 U); CS performance was also studied at a dose of 60 U to permit direct comparison with other pens. A broad range of speed settings was assessed to demonstrate the behavior of the pens during various scenarios.

Of all the pens tested, CS showed the lowest injection force irrespective of injection speeds (constant button speed or constant flow rate). Even at 80 U, the injection force for CS was still lower than the other pens tested at 60 U. These results are consistent with the previous study demonstrating patient preference for CS compared with NP4 and LL.[21] Lower injection force could be an important benefit to patients with diabetes who may have reduced finger joint mobility or limited hand strength as a result of their disease.[17–20]

At injection speeds of 4 and 8 mm/s, CS is associated with low injection forces (6.68 ± 0.44 and 14.11 ± 0.78, respectively). These injection forces compare favorably with those from a study with the Next Generation FlexPen fitted with NovoFine 32 G Tip ETW 6 mm needles where injection forces of 8.3 ± 0.6, 12.0 ± 0.9, and 16.2 ± 1.3 N were measured at injection speeds of 4, 6, and 8 mm/s, respectively.[22]

Differences in injection force have been observed using different needle types, even those with the same gauge.[25] Thus, needle dimensions can affect the performance and thereby the comfort level of a pen. In this study, all pens, except BP, were tested with the manufacturer's recommended needle, the Novofine 31 G × 6 mm from Novo Nordisk for NP4 and the Becton Dickinson Microfine 31 G × 5 mm needle for CS and LL. The latter needle also was used for the BP because it more closely matched the dimension of the Novofine 31 G × 6 mm needle and because preliminary analyses showed that injection forces were lower with the manufacturer's recommended Berlifine 30 G × 8 mm needle from Berlin Chemie compared with the Becton Dickinson Microfine needle. Use of the Berlifine 30 G × 8 mm needle with its different dimensions would have a strong impact upon the ability to compare injection forces between pens. Each of the tested pen types can accommodate both basal and bolus insulins from each manufacturer. The small differences in density of the various insulins, while marginally affecting injection force with the same pen, have no significant impact on the comparison of injection force between the pens.[25]

Clinical Study Considerations

Further studies into the impact of insulin pens on clinical outcomes, compliance, and quality of life have been recommended.[1] The lower injection force of CS may positively influence all three of these factors, but clinical studies will be needed to confirm it. It is also recommended that the injection force of CS be studied in a clinical setting. It should be noted that, while a wide range of button speeds and flow rates were tested in this study, the product label instructions to patients and clinicians recommend that injections be performed slowly and smoothly for accurate dosing, with injection rates not in excess of 10 U/s. A study in patients with diabetes would be beneficial to confirm these recommendations. Together, these studies would provide supporting data to educate physicians on the benefits of insulin pens, as the lack of awareness of insulin pens by primary care physicians has been seen as limiting their introduction.

Conclusions

In this laboratory setting, the CS pen was shown to have a lower injection force at a wide range of different injection speeds than comparable insulin pens. This, in combination with the findings from previous studies,[21] would suggest that the CS pen is likely to provide an important benefit to patients with diabetes, particularly those who may have reduced manual dexterity or strength.

Funding:

This study was funded by sanofi-aventis, Deutschland GmbH.

Acknowledgments:

Editorial support was provided by Tom Claus of PPSI and funded by sanofi-aventis.

Disclosures:

Arnd Friedrichs and Steffen Adler are employees of LWS Risk Management Consult GmbH, a paid consultant to sanofi-aventis. Volker Korger is an employee of sanofi-aventis.

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