Comparison of the Dose Accuracy of Prefilled Insulin Pens

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Abstract

Background:
Prefilled insulin pens have become a convenient and accurate way for diabetes patients to inject insulin. Their ease of use has helped to reduce the resistance of patients with type 1 diabetes and type 2 diabetes in the United States and Europe toward initiation of insulin therapy. This study compared the dosing accuracy of two prefilled insulin pens (the SoloStar® from Sanofi Aventis, Berlin, Germany, and the Next Generation [NG] FlexPen® from Novo Nordisk, Mainz, Germany).

Methods:
The dosing accuracy was tested for both pens with 24 x 10 international units of insulin (IU) and 9 x 30 IU injection volumes to investigate whether the pens comply within the acceptable International Organization for Standardization (ISO) limits of 10% (±1 IU) for 10 IU and 5% (±1.5 IU) for 30 IU. The doses were applied each with a new needle strictly according to the instructions for use of the pen manufacturers. A sensitive pharmaceutical balance was used for the assessment of the applied volumes, and the results were corrected for the specific density of the insulin formulations. We used 18 insulin pens (from two different production lots each) for the two volumes, respectively, resulting in a total of 432 doses per pen with 10 IU and 162 doses per pen with 30 IU.

Results:
Both pens showed a very good performance, which was better for the 10 IU dose than in comparative previous studies. The NG FlexPen (mean absolute percent deviation 10 IU/30 IU: 1.63 ± 0.84%/1.23 ± 0.76%) was even more accurate than the SoloStar (2.11 ± 0.92%/1.54 ± 0.84%, p < .001/p < .05 versus the NG FlexPen). Only 0.2% of the doses were outside the ISO limit at 10 IU, with the NG FlexPen (0.6% at 30 IU). The corresponding figures for the SoloStar were 0.4% and 1.8%, respectively.

Conclusions:
A direct head-to-head comparison of the two prefilled insulin pens with a standardized protocol resulted in a more stable dosing accuracy of both pens as compared to previous investigations. In this investigation, the NG FlexPen was more accurate than the SoloStar at both tested doses.


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Abbreviations: (ISO) International Organization for Standardization, (IU) international unit [of insulin], (NG) Next Generation

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Introduction

In the past, insulin was generally delivered via injection with vial and syringe, but the newer injection pens are increasingly used in the developed world. They have a number of advantages over the traditional vial and syringe method, which can be cumbersome to use and can be associated with needle anxiety, fear of injection pain, and social embarrassment. Given the complex insulin regimens that many patients will be using (basal insulin injections plus more frequent short-acting insulin injections), the ease of use and patient friendliness nature of prefilled pen injection systems may improve adherence to treatment regimens or may make patients with type 2 diabetes less reluctant to start insulin therapy. In consequence, several prefilled disposable insulin pens have been developed to address these medical needs.

The FlexPen® (Novo Nordisk, Mainz, Germany) is a widely used prefilled insulin delivery pen for patients with type 1 or type 2 diabetes. Well-designed trials suggest that the FlexPen is more accurate than other prefilled pens at high, medium, and low doses. Furthermore, the FlexPen is preferred to vial and syringe by patients, but comparisons of patient preference for different pens are currently lacking. The FlexPen improves adherence and reduces costs compared with vial and syringe, but the relative adherence/cost benefits of different pens are unknown. These features have made the FlexPen one of the most popular insulin injection devices in the world.

Recent changes have been made to the design of the FlexPen, including, but not limited to, the visual appearance of the pen, cartridges, and packaging to help differentiate insulin types and the push button mechanism to reduce injection force. It is expected that the Next Generation (NG) FlexPen has similar accuracy to the FlexPen but has improved patient perception. The present study was performed to investigate the dosing accuracy of the NG FlexPen in comparison to the SoloStar® (Sanofi Aventis, Berlin, Germany) prefilled insulin injection device.

Research Design and Methods

The NG FlexPen is a prefilled 3 ml pen device available for injection of insulin aspart, biphasic insulin aspart, and insulin detemir. The SoloStar is a prefilled 3 ml device for insulin glargine administration. For this experiment, 36 pens from two different production lots (18 each) were obtained through a local pharmacy (SoloStar) and through an international pharmacy from France (NG FlexPen), respectively, to avoid selection bias by the manufacturers. Dosing accuracy was tested by emptying 3 ml cartridges with 24 x 10 international units of insulin (IU) or 9 x 30 IU injection volumes, respectively. It was investigated whether the pens comply with the acceptable dose accuracy limits of 10% (±1 IU) for 10 IU and 5% (±1.5 IU) for 30 IU, as set forth by International Organization for Standardization (ISO) regulations (ISO 11608-1:2000). The needles used for this evaluation were chosen following the recommendations of both manufacturers of the insulin pens (NovoFine 31 gauge 6 mm needles for the FlexPen and BD Micro-Fine 31 gauge 5 mm needles for the SoloStar device).

A new needle was applied followed by a priming procedure (2 IU) prior to every dose, which was delivered strictly according to the instructions for use for both devices. A sensitive pharmaceutical balance was used for the assessment of the applied volumes (AX205 Delta Range, Mettler Toledo), and the results were corrected for the specific density of the insulin formulations (insulin glargine, 1.004 g/ml; insulin detemir, 1.014 g/ml, measured at 20 °C). We used 18 insulin pens from two different lots each for the two volumes, respectively, resulting in a total of 432 doses per pen with 10 IU and 162 doses per pen with 30 IU. The experiments were performed in two fractions of 9 pens/doses each, with two different investigator groups. All investigators of this study were trained and experienced in accurate delivering of very small volumes by means of pipettes, syringes, and pen devices. One team (A. Weise, J. W. Pfützner, H. Hänel, and A. Pfützner) had performed a comparable pen accuracy experiment previously (comparing four pens including SoloStar and the original FlexPen), while the other team (J. Borig, A. M. Pfützner, M. Safinowski, and P. B. Musholt) had no previous experience with this particular type of experiment.

Outcome measures were the accuracy of dose delivery from the two pens in comparison with the specified dose (analyzed by nonparametric Wilcoxon rank test) and the failure number to achieve the required accuracy specifications (two-sided Wilcoxon rank test for two independent samples). The statistical analyses were performed using SPSS12.0 (SPSS GmbH Software, Munich, Germany), and a p value <.05 was considered to be of statistical significance.
Results

The mean dosing accuracies of both pens were in the range of the defined borders. With a dose of 10 IU, the NG FlexPen exhibited significantly lower deviations than the SoloStar (NG FlexPen, 1.63 ± 0.85%; SoloStar, 2.11 ± 0.56% \([p < .001\) versus NG FlexPen]). A corresponding result was found for the 30 IU doses (NG FlexPen, 1.23 ± 0.66%; SoloStar, 1.58 ± 0.62% \([p < .05\) versus NG FlexPen]). The comparison between the pen devices is presented in Figure 1. No overdosing above the defined thresholds occurred with any of the pens. Underdosing beyond the defined thresholds took place only in very few cases with the SoloStar (10 IU, 2 [0.4%]; 30 IU, 3 [1.8%]) and even less with the NG FlexPen (10 IU, 1 [0.2%]; 30 IU, 1 [0.6%]). Overall, both pens showed no systematic deviations as shown in Figures 2 and 3. There were no differences in the results between the two investigator groups.

Discussion

Pen devices with high dosing accuracy are an important tool to contribute to an improved treatment safety. Two types of insulin pens are currently available in the United States and Europe: disposable and reusable pens. Both types consist of an insulin cartridge or refill with its own needles, which are changed after each application. As an increasing amount of delivery systems are introduced by all the major insulin producers (e.g., NovoPen 4®; Novo Nordisk; SoloStar®, Sanofi Aventis; HumaPen®Luxura, Lilly) in response to an ever-increasing amount of patients treated with insulin, emphasis must be
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put on device manufacturers to ensure an important but evident task: delivering the correct amount of insulin to the patients in an easy, convenient way.

The prefilled FlexPen is currently available in many countries and has become one of the most popular pen devices worldwide. Recent changes have been made to the design of the FlexPen, such as improvements in the visual appearance of the pen, cartridges, and packaging to help differentiate insulin types and the push button mechanism to reduce injection force. The dose accuracy of the NG FlexPen has already been tested and compared with FlexPen. Using the method of delivering insulin doses onto a precision balance showed that the NG FlexPen maintains the excellent accuracy of the FlexPen. Neither pen delivered any doses of 1 IU, 30 IU, or 60 IU outside predefined limits (180 doses delivered with each pen), and deviation from the intended doses was very low for the FlexPen (0.06 IU, 0.23 IU, and 0.36 IU at 1 IU, 30 IU, and 60 IU, respectively). The injection force with the NG FlexPen (12.6 N) is approximately 30% lower than with the FlexPen (17.9 N). These values were means of 20 pens measured under standard temperature and humidity conditions, and the range of injection forces measured with the NG FlexPen (10.6–18.6 N) were consistently lower than with the FlexPen (15.4–20.0 N). Importantly, the injection force with the NG FlexPen is lower than with the SoloStar at a range of injection speeds. The direct comparison also showed that the FlexPen took less time to deliver 60 IU than the SoloStar at all three injection speeds—a factor that could potentially improve the discreetness of the pen.

Our direct comparison of the accuracy of insulin delivery pens by means of a standardized laboratory protocol showed a very good performance of the prefilled pen
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devices, which were both matching the specifications of the ISO requirements. Like in previous investigations with the FlexPen,\textsuperscript{10–14} the prefilled NG FlexPen had a significantly better accuracy when delivering insulin detemir than the SoloStar when delivering insulin glargine. While no overdosing was seen with any of the devices, underdosing occurred in a few cases.

A weakness of our study is that we had to assess the dosing accuracy in an in vitro setting by means of a pharmaceutical balance. While we have been able to assess the technical dose delivery accuracy, it is possible that a clinical subcutaneous insulin administration may result in different device performance. However, it is very important that patients and physicians have confidence in the accuracy of their chosen insulin pen. This is a prerequisite for a good metabolic control, regardless of the pen type used.\textsuperscript{2}

In conclusion, the NG FlexPen and the SoloStar showed a good performance, but ultimately, the NG FlexPen had more accurate dosing results.

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