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ORIGINAL ARTICLES

Differences in the Dose Accuracy of Insulin Pens

Heike Hänel, M.Sc., Alexander Weise, M.Sc., Wei Sun, M.Sc., Johannes W. Pfützner, Nicole Thomé, Ph.D., and Andreas Pfützner, M.D., Ph.D.

Abstract

Background:

Modern insulin injection pens provide a convenient and accurate way for diabetes patients to inject insulin. They have widespread use among children and adults with type 1 and type 2 diabetes in the U.S. and Europe. This study compared the dosing accuracy of four commonly available insulin pens (OptiClik® and SoloSTAR® from sanofi-aventis, FlexPen® from Novo Nordisk, and HumaPen® LUXURA™ from Eli Lilly).

Methods:

The dosing accuracy was tested for all pens with 24 x 10 IU and 9 x 30 IU injection volumes to investigate whether the pens complied with 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 each applied with a new needle strictly according to the instructions for use by the pen manufacturers. A pharmaceutical balance was used for the assessment of the applied volumes, and the results were corrected for the specific density of the insulin formulations. Four insulin pens (two each from different production lots) were used for each of the two volumes, resulting in a total of 192 doses per pen with 10 IU, and 72 doses per pen with 30 IU.

Results:

FlexPen (mean absolute percent deviation for 10 IU and 30 IU: 1.64 ± 0.84% and 0.83 ± 0.26%, respectively) and HumaPen LUXURA (1.10 ± 0.20% and 0.62 ± 0.19%; not significant versus FlexPen for both doses) were more accurate than the OptiClik (4.78 ± 3.31% and 2.97 ± 2.48%, $p < .01$) and the SoloSTAR (2.61 ± 0.92% and 1.70 ± 0.84%, $p < .05$). While 6.8% of doses were outside the ISO limit at 10 IU with OptiClik (13.9% at 30 IU), the corresponding figures were 0.5% and 4.1%, respectively, for SoloSTAR. No doses outside the ISO limits were seen with FlexPen or HumaPen LUXURA at 10 IU and only one 30 IU dose (1.4%) was outside the limit for FlexPen.

Conclusions:

A direct head-to-head comparison of four insulin pens with a standardized protocol resulted in a more stable dosing accuracy of the FlexPen and the HumaPen LUXURA in comparison to the OptiClik and SoloSTAR. Even though all insulin delivery systems undergo rigorous testing before being approved for sale, there may be reasons to be attentive to the performance of the devices in practical use.

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Author Affiliation: Institute for Clinical Research and Development, Mainz, Germany

Abbreviations: (IDDM) insulin dependent diabetes mellitus, (NPH) neutral protamine Hagedorn, (n.s.) not significant

Keywords: accuracy, disposable pen, dose delivery, insulin, reusable pen

Corresponding Author: Prof. Andreas Pfützner, M.D., Ph.D., Department of Research and Development, Institute for Clinical Research and Development, Parcusstrasse 8, D-55116 Mainz, Germany; email address *andreasp@ikfe.de*

Introduction

Patients with insulin-dependent diabetes mellitus (IDDM) are challenged nowadays with a wide variety of self-monitoring tasks, i.e., daily performance of preprandial blood glucose readings, consecutive performance of insulin dose calculations, as well as insulin administration. Since the introduction of the first pen devices for easier insulin administration in the 1990s, it has been shown that insulin pens improve the quality of life of IDDM patients[1] by providing a more convenient and accurate way of insulin delivery than common insulin syringes. The patient preference for insulin pens compared to syringes has been the subject of several previous studies, with the consistent finding that ease of use, discreetness, flexibility, and convenience make them the preferred way of insulin administration.[2-6]

The widespread acceptance of pen devices among adults and children in the U.S., Europe, and Japan demands for devices with very easy and error-free handling, and high accuracy in dose delivery. Insulin pens should be accurate and precise, especially for low-dose administration.[7] While many, especially older patients, use prefilled pen devices, some insulin pen models have a refill system so that they can be used over a period of several months or even years, which requires a high quality product line in terms of stability and accuracy.[8]

A previous study in Japan[9] and an additional report from the U.S.[10] indicated some potential problems with at least one of these frequently used pen injection systems—the OptiClik from sanofi-aventis—with regard to dose delivery accuracy. This investigation was performed to establish the dosing accuracy of four currently, commercially available pen injection systems in a controlled laboratory setting (FlexPen®, NovoNordisk, Mainz; OptiClik®, sanofi-aventis, Berlin; SoloSTAR®, sanofi-aventis, Berlin; and HumaPen® LUXURA™, Eli Lilly, Bad Homburg).

Research Design and Methods

The FlexPen is a prefilled pen and is available for injection of insulin aspart, biphasic insulin aspart, and insulin detemir. The OptiClik is a reusable pen device for injection of insulin glulisine and insulin glargine. SoloSTAR is a prefilled device for insulin glargine administration, and HumaPen LUXURA is a refillable pen for injection of neutral protamine Hagedorn (NPH) insulin and insulin lispro. The experiments were performed for two doses (10 IU and 30 IU) with eight pens for each dose, derived from two different production lots (four pens/dose/lot). FlexPen (Lot# SP51312 and SP51572) containing insulin detemir (Levemir®, NovoNordisk, Mainz); SoloSTAR (40N001, 40N002) containing insulin glargine; OptiClik (40N029, 40N070) used with 3 ml insulin glargine cartridges (Lantus®, sanofi-aventis, Berlin); and HumaPen LUXURA (A331356, A353118) filled with 3 ml NPH insulin (Huminsulin Basal®, Eli Lilly, Bad Homburg), were obtained from the stock of a local pharmacy in Düsseldorf, Germany, to avoid lot selection bias by any of the manufacturers. The dosing accuracy was tested by emptying 3 ml cartridges with 24 x 10 IU and 9 x 30 IU injection volumes. It was investigated whether the pens complied with the acceptable limits of 10% (± 1 IU) for 10 IU and 5% (± 1.5 IU) for 30 IU, as set forth by the International Organization for Standardization guidelines (ISO 11608-1:2000[11]). The needles used for this evaluation were chosen following the recommendations of the 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 OptiClik, SoloSTAR, and HumaPen LUXURA). A new needle was applied followed by a priming procedure (2 IU) for every dose, which was delivered strictly according to the instructions for use for both devices. A pharmaceutical balance was used for the assessment of the applied volumes (AX205 Delta Range, Mettler Toledo, Giessen, Germany), 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; NPH insulin, 1.008 g/ml; all measured at 20 °C). Eight insulin pens each from two different lots were used for the two volumes, resulting in a total of 192 doses per pen with 10 IU, and 72 doses per pen with 30 IU. The investigators of this study were trained and experienced in accurate delivery of very small volumes by means of pipettes, syringes, and pen devices. Outcome measures were the accuracy of dose delivery from the four pen types in comparison with the specified dose (analyzed by nonparametric Wilcoxon signed-rank test), and the number of pens that failed to achieve the required accuracy specifications (two-sided Wilcoxon signed-rank test for two independent samples). The statistical analyses were performed using SPSS12.0 (SPSS GmbH Software, Munich), and a p value of $<.05$ was considered to be of statistical significance.

Results

The mean dosing accuracies of all pens were in the range of the ISO defined borders. With a dose of 10 IU, the FlexPen and the HumaPen LUXURA exhibited significantly

lower deviations than the OptiClik or SoloSTAR (FlexPen, 1.64 ± 0.84%; HumaPen, 1.10 ± 0.20%, not significant (n.s.) vs FlexPen; OptiClik, 4.78 ± 3.31%, p <.01 vs FlexPen and HumaPen LUXURA; and SoloSTAR, 2.61 ± 0.92%, p <.05 vs FlexPen, HumaPen LUXURA, and OptiClik). A corresponding result was found for the 30 IU doses: FlexPen, 0.83 ± 0.26%; HumaPen LUXURA, 0.62 ± 0.19%, n.s. vs FlexPen; OptiClik, 2.97 ± 2.48%, p <.01 vs FlexPen; and HumaPen LUXURA; SoloSTAR, 1.70 ± 0.84%, p <.05 vs FlexPen and HumaPen LUXURA). 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 in several cases with the OptiClik (13 (6.8%) at 10 IU; 10 (13.9%) at 30 IU). It occurred in particular at the beginning of dose delivery as shown in **Figure 2** and **Figure 3**. In this analysis, the SoloSTAR (1 (0.6%) at 10 IU; 3 (4.2%) at 30 IU) showed a much better performance than the OptiClik, which was the subject of two previous reports reporting accuracy issues with this device.[8,9] No underdosing was seen with the FlexPen at 10 IU (see **Figure 2**) and only one initial underdosing (1.4%) was seen at 30 IU (one dose of 28.5 IU). Also, no underdosing below the ISO thresholds occurred with the HumaPen LUXURA, neither at 10 IU nor at 30 IU.

Discussion and Conclusions

Interest in intensive insulin therapy has contributed to the increased popularity of alternative insulin delivery systems, including insulin pen delivery devices. Insulin pen injectors were introduced in the mid-1980s. They represented a remarkable advance in the method of insulin administration since they optimized the treatment of type 1 diabetes.[12] Several studies have consistently shown that patients prefer insulin pens to syringes and vials, because of ease of use, flexibility, convenience, and discreetness.[2-7] Even though all insulin delivery systems undergo rigorous testing before being approved for sale, it seems there may be reason to be attentive to the performance of the devices in practical use. The intrapatient variability of insulin action after subcutaneous insulin injection is orchestrated by several physical and technical factors, including but not limited to temperature, injection site, dosing accuracy, and insulin absorption. Variability of insulin absorption has been reported to be around 30% for short-acting insulin and up to 50–60% for long-acting insulin.[13] Pen devices with high dosing accuracy are, therefore, important tools that contribute to improved treatment safety. Two types of insulin pens are currently available in the U.S. and E.U.: disposable and reusable. Both pen types consist of

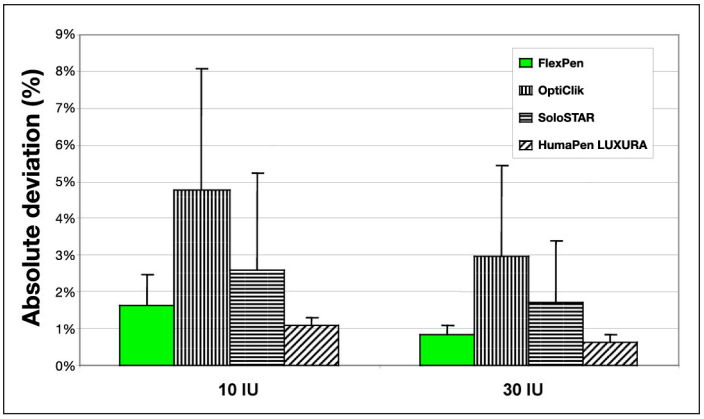

Figure 1. Dose accuracy off all four pen devices as calculated from the mean. Absolute percent deviation (mean ± SD).

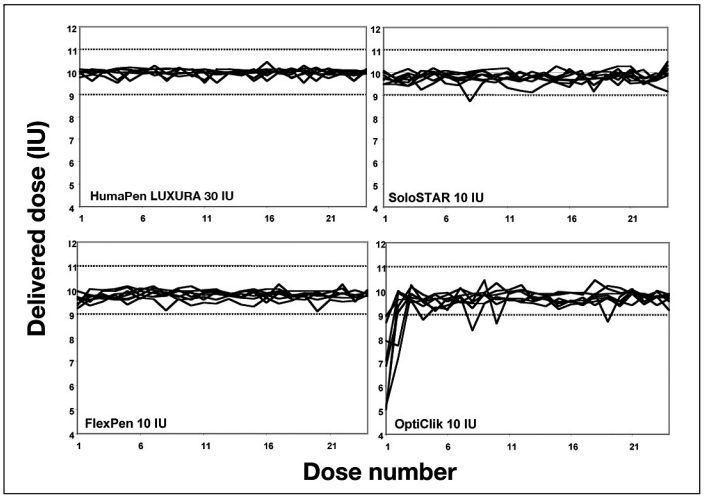

Figure 2. Dose accuracy of the insulin pens at 10 IU (consecutive doses of eight pen devices each; dotted lines represent the limits of the ISO acceptance range).

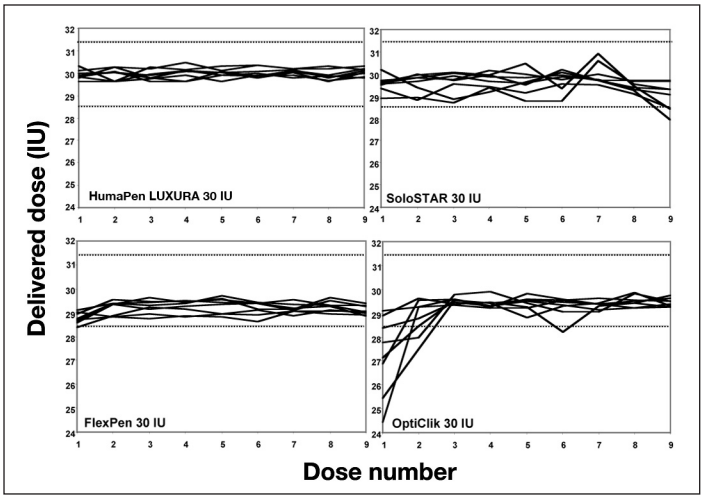

Figure 3. Dose accuracy of the insulin pens at 30 IU (consecutive doses of eight pen devices each; dotted lines represent the limits of the ISO acceptance range).

an insulin cartridge or refill with its own needles, which are changed after each application. As an increasing number of delivery systems are introduced by all the major insulin producers (i.e., NovoPen 4®, Novo Nordisk; SoloSTAR, sanofi-aventis; HumaPen LUXURA, Eli Lilly) in response to an ever increasing number of patients treated with insulin, emphasis must be put on device manufacturers to ensure an important task: delivering the correct amount of insulin to patients in an easy and convenient way.

Our direct comparison of the accuracy of insulin delivery pens by means of a standardized laboratory protocol showed that the prefilled FlexPen and the reusable HumaPen LUXURA had a significantly better accuracy when delivering insulin detemir and NPH insulin, respectively, than the OptiClick or the SoloSTAR when delivering insulin glargine. While no overdosing was seen with any of the devices, underdosing with OptiClik occurred in the majority of the cases within the first quarter of cartridge emptying, despite appropriate needle priming for all doses. This finding is in line with the reports from Nayak and Clement,[10] who also saw this phenomenon in three out of five tested OptiClik devices with the first few doses. It may potentially be avoided by a "system initiation" with into-the-air injection of a larger dose (10–20 IU) at the beginning of the cartridge use.

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 explore the technical dose delivery accuracy, it is possible that a clinical subcutaneous insulin administration may result in different device performance. However, we believe that the technical device performance is the starting "seed" of the overall variability of insulin absorption observed after injection.

It is very important that patients and physicians have confidence in the accuracy of their chosen insulin pen. This is a prerequisite for good metabolic control, regardless of the pen type used.[14] For delivery of insulin glargine, the prefilled SoloSTAR appears to have a superior accuracy to the reusable OptiClik device. The type of pen, however, does not predict accuracy because both the prefilled FlexPen (when delivering insulin detemir) and the reusable HumaPen LUXURA (when delivering NPH insulin) were more accurate than the other two pen devices in our investigation.

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Disclosure:

Andreas Pfützner is a member of the Scientific Advisory Board of Novo Nordisk, Copenhagen, Denmark.

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