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Accuracy and Injection Force of the Gla-300 Injection Device Compared With Other Commercialized Disposable Insulin Pens

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Abstract

Background: To deliver insulin glargine 300 U/mL (Gla-300), the widely used SoloSTAR® pen has been modified to allow for accurate and precise delivery of required insulin units in one-third of the volume compared with insulin glargine 100 U/mL, while improving usability. Here we compare the accuracy and injection force of 3 disposable insulin pens: Gla-300 SoloSTAR®, FlexPen®, and KwikPen™.

Methods: For the accuracy assessment, 60 of each of the 3 tested devices were used for the delivery of 3 different doses (1 U, half-maximal dose, and maximal dose), which were measured gravimetrically. For the injection force assessment, 20 pens of each of the 3 types were tested twice at half-maximal and once at maximal dose, at an injection speed of 6 U/s.

Results: All tested pens met the International Organization for Standardization (ISO) requirements for dosing accuracy, with Gla-300 SoloSTAR showing the lowest between-dose variation (greatest reproducibility) at all dose levels. Mean injection force was significantly lower for Gla-300 SoloSTAR than for the other 2 pens at both half maximal and maximal doses ($P < .0271$).

Conclusion: All tested pens were accurate according to ISO criteria, and the Gla-300 SoloSTAR pen displayed the greatest reproducibility and lowest injection force of any of the 3 tested devices.

Keywords

accuracy, Gla-300 SoloSTAR, injection force, insulin pen

Insulin injection pens, introduced in the 1980s, have led to greater compliance with insulin therapy[1] and are generally preferred by people with diabetes over vials and syringes.[2] In addition, insulin pens deliver more accurate and consistent doses of insulin than vials and syringes[3-5] and their use has been found to correspond with better glycemic control and reduced hypoglycemia.[6,7]

To further improve the confidence of pen users, advances in pen device technology are continuously being made. For example, reducing the amount of force required to depress the pen injection button is an important aspect of improving the ease of pen use,[8] especially with high doses and in people with limited ability to self-inject insulin. The insulin glargine 100 U/mL (Gla-100; Lantus®) SoloSTAR® disposable pen device (Sanofi, Paris, France) was developed on the basis of unmet user needs, such as ease of injection and short dial stroke, even when injecting higher insulin volumes. Since its launch in 2007, Gla-100 SoloSTAR has demonstrated comparable dose accuracy with the FlexPen® (Novo Nordisk A/S, Bagsværd, Denmark) and KwikPen™ (Eli Lilly & Co, Indianapolis, IN),[9] but with a lower injection force.[8]

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Table 1. Mean Actual Doses and Deviation From Target Doses, by Pen Type.

		Actual dose (U)						
Insulin pen	Target dose (U)	Min	Max	Mean dose	SD	CV (%)	Mean deviation (U)	Mean relative deviation (%)
Gla-300 SoloSTAR	1	0.93	1.34	1.11	0.09	8.49	0.11	10.86
FlexPen	1	0.81	1.25	1.06	0.09	8.61	0.07	6.46
KwikPen	1	0.88	1.27	1.09	0.10	8.92	0.09	8.72
Gla-300 SoloSTAR	40	39.08	40.30	39.71	0.26	0.65	−0.29	−0.72
FlexPen	30	28.93	30.35	29.53	0.29	0.97	−0.47	−1.56
KwikPen	30	29.40	30.32	29.87	0.24	0.81	−0.13	−0.43
Gla-300 SoloSTAR	80	78.37	80.21	79.43	0.46	0.58	−0.57	−0.72
FlexPen	60	58.10	59.98	59.13	0.47	0.80	−0.88	−1.46
KwikPen	60	58.78	61.70	59.72	0.51	0.85	−0.28	−0.46

A new insulin glargine comprising 300 U/mL (Gla-300, Toujeo®) has been developed, and has recently been approved for use in the United States,[10] in Europe[11], in Canada,[12] in Australia,[13] and in Japan. Gla-300 comprises the same number of insulin glargine units in only one-third of the volume compared with Gla-100. Like Gla-100, Gla-300 employs subcutaneous precipitation as a retarding principle.[14] Gla-300 is thought to have a lower redissolution rate from the subcutaneous depot, and has been found to provide more stable and prolonged pharmacokinetic and pharmacodynamic profiles, compared with Gla-100.[14] In clinical trials this has been shown to result in equivalent glycemic control with Gla-300 versus Gla-100, but with a lower risk of hypoglycemia.[15-17] Speculatively, since large doses of insulin are often required to attain blood glucose control, especially in people with insulin resistance, the lower injection volume requirement of Gla-300 may be beneficial in reducing injection site discomfort.

To administer Gla-300, the Gla-100 SoloSTAR pen has been modified. While there have been no changes in user tasks and dose settings from SoloSTAR to Gla-300 SoloSTAR (Sanofi; both pens allow for multiple doses and deliver a maximum single dose of 80 U, in 1 U increments), certain pen features have been enhanced to optimize usability.[18] These features include technical modifications that, for a given dose, retain the same push button dial stroke as the Gla-100 SoloSTAR pen while reducing the travel of the plunger to accommodate a lower insulin volume, which should reduce the force needed to inject.

Here we investigate the dosing accuracy and injection force of the new Gla-300 SoloSTAR compared with Levemir® U100 FlexPen (Novo Nordisk A/S, Bagsværd, Denmark) and Humalog® U100 KwikPen (Eli Lilly & Co, Indianapolis, IN) when injecting various dose levels.

Methods

Materials and Methods

Dose Accuracy. An overview of the insulin pens and corresponding needles used is provided in Supplementary Table 1. In total, 60 previously unused pens of each type were used for the delivery of each dose level at ambient temperature; low (1 U), half-maximal dose (HMD; 40 U for Gla-300 SoloSTAR, and 30 U for FlexPen and KwikPen) and maximal dose (MD; 80 U for Gla-300 SoloSTAR and 60 U for FlexPen and KwikPen). Pens were operated according to the manufacturer's instructions.

The low dose, HMD, and MD were dispensed from each pen in a randomized manner, according to the schematic diagram presented in Supplementary Figure 1. Three recorded doses were therefore dispensed from each pen, generating 180 values for each pen type. All measurements were performed by a single investigator to eliminate potential user variability. For each dose delivery, a new needle was used and the pen was primed in accordance with manufacturer's recommendations. After removing the protective cap and attaching the needle, 2 priming doses of 2 U (3 U for Gla-300 SoloSTAR) were discarded in a separate beaker. The priming dose was repeated if necessary until insulin was dispensed from the pen. Prior to each gravimetrically measured dose, a "skip" dose (an aliquot of insulin that was not measured for the purposes of dosing accuracy, but that was evacuated between measured test doses to ensure that these were randomly dispensed from either the front, middle or rear area of the cartridge) was delivered into a separate beaker and discarded, followed by attachment of a new needle and priming (Supplementary Figure 1).

Each recorded dose was dispensed in a 20 mL beaker containing a 0.5-1 cm layer of liquid paraffin, covered with parafilm. When dispensed, the plunger was depressed for 5 seconds for Gla-300 SoloSTAR, 6 seconds for FlexPen, and 5 seconds for KwikPen (in accordance with manufacturer's instructions) to ensure that the dialed dose was fully expelled. If an insulin drop remained at the tip of the needle, the drip was stripped off at the paraffin surface without touching the needle to the paraffin.

Each recorded dose was weighed by a Mettler Toledo analytical balance type XP205/M for FlexPen and KwikPen, and type XP56/M for Gla-300 SoloSTAR (Mettler-Toledo Inc, Columbus, OH), with a weighing accuracy of 0.01 mg and

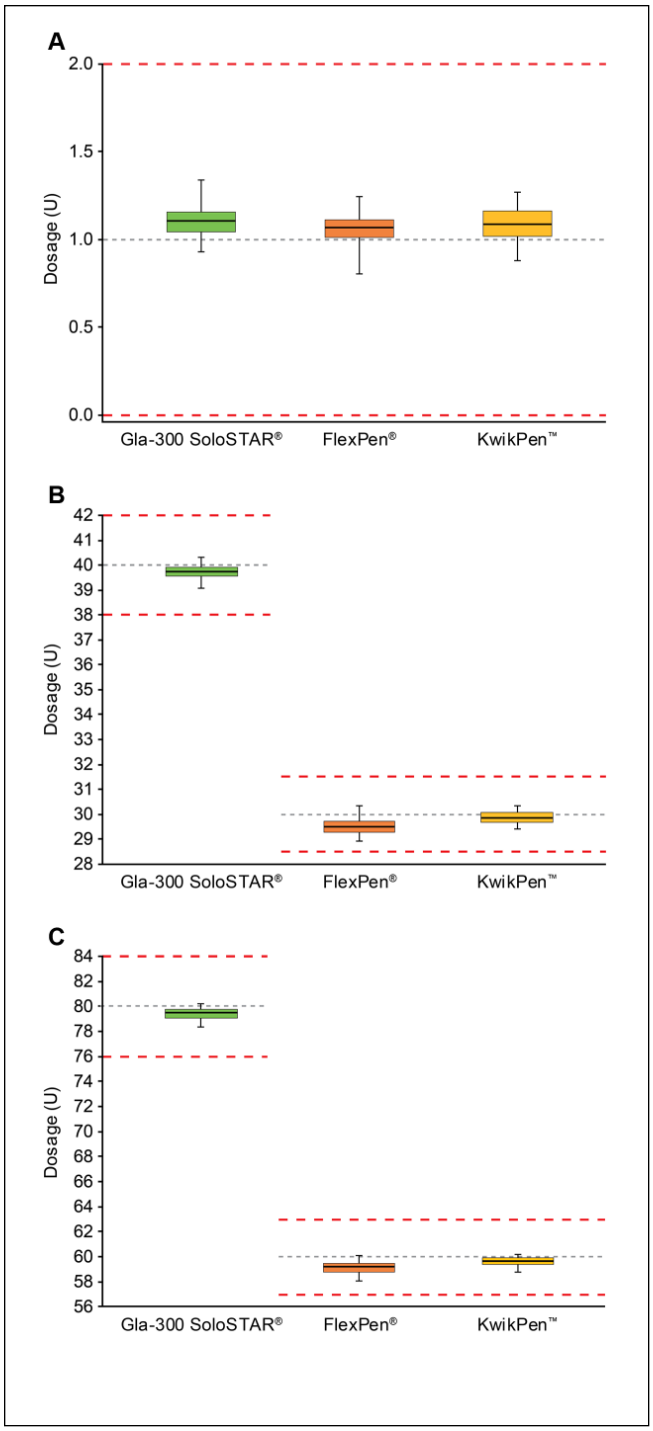

Figure 1. Distribution of actual doses categorized by pen type at the (A) 1 U, (B) half-maximal dose (30/40 U), and (C) maximal dose (60/80 U) levels. The red dashed lines represent the ISO limits, while dashed gray lines represent the target dose. Boxes represent the median with 25th and 75th percentiles, and whiskers represent minimum and maximum values.

0.001 mg, respectively. The beaker containing the liquid paraffin layer was placed on the balance and zeroed before each insulin dose was dispensed and weighed. All generated data were transferred into Excel by the LabX pro balance software Version 1.0 (Mettler-Toledo Inc), except for Gla-300 SoloSTAR, for which data were transferred manually because the type XP56/M balance was not linked to the LabX software.

Prior to the study, the density of the insulin preparations was determined using a DMA 4500 density meter (Anton Paar GmbH, Bruchköbel, Germany). The specific density (g/cm^3) was 1.0075 for Gla-300 SoloSTAR, 1.0095 (Batch DH70708) or 1.0096 (Batch DH70813) for FlexPen, and 1.0062 for KwikPen. To accurately estimate the volume of dispensed insulin, the weights of the respective insulin doses were corrected for this specific density, as well as the concentration of each insulin.

Injection Force. An overview of the insulin pens and corresponding needles used is provided in Supplementary Table 1. Injection force was measured at the HMD and MD dosing level for each pen (40/80 U for Gla-300 SoloSTAR and 30/60 U for FlexPen and KwikPen), at an injection speed of 6 U/s. At each dose setting 20 new pens of each type were tested, each individual pen being tested twice at HMD and once at MD according to a replicate plan, generating 40 values for HMD and 20 values for MD. All pens were primed before each dose delivery. Force was measured throughout the dose delivery. The mean maximum and mean plateau forces were calculated for each pen type. Injection forces were measured in newtons (N) using an isometric injection with a Zwick Z2.5 testing machine and a Zwick Xforce KAF load cell (Zwick Roell GmbH & Co, Ulm, Germany) under standard atmospheric conditions. All investigations were conducted using the manufacturers' recommended needles.

Statistical Analyses

Evaluation of dose accuracy was based on the recommendation of the International Organization for Standardization (ISO; DIN EN ISO 11608-1:2012).[19] An injector population meets the criteria for dosing accuracy if the statistical tolerance interval (the mean of the individual values plus or minus the standard deviation, multiplied by a tolerance limit factor [$k = 2.670$ based on a 95% confidence interval and the number of pens tested]) lies within ISO acceptance limits. These acceptance limits are defined as ±1 U for target doses of <20 U, and ±5% for target doses >20 U, corresponding to the following limits for low, HMD, and MD dose levels: 1.0 ± 1.0 U (0.0-2.0 U), 40.0 ± 2.0 U (38.0-42.0 U), and 80.0 ± 4.0 U (76.0-84.0 U) for Gla-300 SoloSTAR; and 1.0 ± 1.0 U (0.0-2.0 U), 30.0 ± 1.5 U (28.5-31.5 U), and 60.0 ± 3.0 U (57.0-63.0 U) for FlexPen and KwikPen.

From actual dose measurements the standard deviation (SD) and coefficient of variation (CV) of actual doses (between-dose variation; reproducibility), and both the average absolute and relative (%) deviations from the target dose, were calculated. Because of the volumetric difference, 1 unit of Gla-300 is equivalent to one-third of the volume of Levemir U100 and Humalog U100; a test for statistical

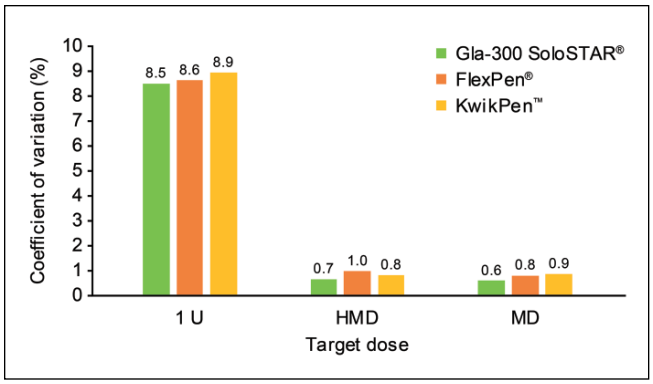

Figure 2. Reproducibility (between-dose coefficient of variation) across each dose level by pen type. HMD, half-maximal dose (30/40 U); MD, maximal dose (60/80 U).

significance between the tested pen types was therefore not viable.

Statistical significance of the differences in injection force (mean maximum and plateau force) between Gla-300 SoloSTAR and each of the comparator pens was estimated using Dunnett's test. Compared means were assumed to be different, with a probability of at least 97.29% ($P < .0271$), if the confidence interval of the mean difference did not include zero.

Results

Dose Accuracy

All 3 tested pens met the ISO acceptance criteria for dosing accuracy (DIN EN ISO 11608-1:2012)[19] at ambient temperature. Calculated statistical tolerance intervals were within the ISO acceptance range for all pens at all dose levels (Supplementary Table 2), as were individual doses (Figure 1).

At the HMD and MD dose levels, all pens displayed a low deviation of the average actual dose from the target dose. Gla-300 SoloSTAR showed a deviation (both absolute and relative) that was less than that of FlexPen but greater than that of KwikPen (Table 1).

Between-dose variation (CV) was similar for all tested pens, but lowest for Gla-300 SoloSTAR at all dose levels (Figure 2). CV estimates were considerably higher for all pens at the 1 U dose level (8.5-8.9%) than at the HMD and MD levels (0.6-1.0%).

Injection Force

Both the mean plateau injection force and the mean maximum injection force for Gla-300 SoloSTAR were significantly lower ($P < .0271$) than those measured for the other 2 tested pens, at both HMD (30/40 U) and MD (60/80 U) (Figure 3; Supplementary Table 3). The force discrepancy between maximum injection force and plateau force was lowest for Gla-300 SoloSTAR (Supplementary Table 3).

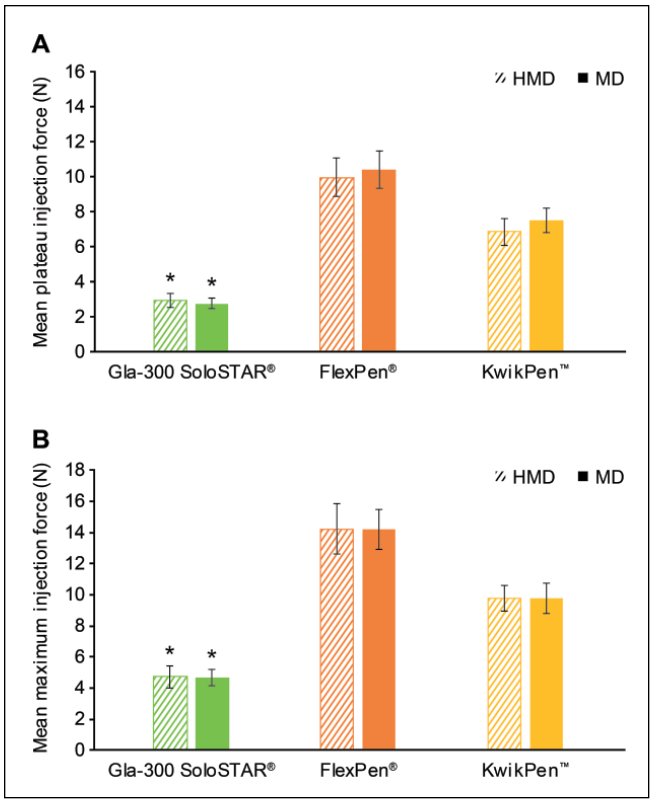

Figure 3. Mean (SD) plateau (A) and maximum (B) injection force at half-maximal dose (HMD; 30/40 U) and maximal dose (MD; 60/80 U) levels. *$P < .0271$ vs individual pens at both dose levels.

Discussion

To accommodate new insulin glargine 300 U/mL (Gla-300), which contains the same number of insulin units in one-third of the volume as glargine 100 U/mL (Gla-100), the SoloSTAR pen has been modified while retaining its functional properties. In this study Gla-300 SoloSTAR demonstrated excellent dosing accuracy according to ISO criteria,[19] at 3 dose levels, and all individual doses were within the ISO limits. Compared with FlexPen and KwikPen at both HMD and MD dose levels, the Gla-300 SoloSTAR pen also displayed similarly small deviations in the actual dose delivered relative to the target dose. Furthermore, Gla-300 SoloSTAR was associated with the lowest between-dose CV (highest reproducibility) of all tested pens at all dose levels, despite Gla-300 necessitating a lower injection volume than delivered by all other pens. From a clinical perspective, accuracy and improved reproducibility of dosing could be advantageous in diabetes management, potentially allowing people with diabetes to more accurately titrate their insulin dose to the optimal level for glycemic control with a reduced risk of hypoglycemia or hyperglycemia.

The lower injection force required with Gla-300 SoloSTAR, at both HMD and MD dose settings, is of interest and suggests that this insulin pen could offer improved usability and may benefit those with reduced hand strength. HMD and MD were

higher for Gla-300 SoloSTAR (80 U and 40 U, respectively) than for the 2 other tested pens (60 U and 30 U for both pens), so it is possible that measuring injection force at equal doses would increase the observed difference between the injection force required with Gla-300 SoloSTAR versus FlexPen and KwikPen. In addition, Gla-300 SoloSTAR shows advantages with respect to a smooth uniform force path, indicated by the lowest force discrepancy between maximum injection and plateau force compared with FlexPen and KwikPen. The injection force results are corroborated by the opinions of both pen users and trainers during an interview-based survey, who rated Gla-300 SoloSTAR as requiring the least effort to press the plunger.[18] The low levels of force needed to inject insulin with Gla-300 SoloSTAR are a result of the smaller volume of Gla-300 per unit of insulin compared with the insulin dispensed by the other tested pens, and the technical modifications made to reduce the travel of the plunger while retaining the same push button dial stroke, which are directly aimed at improving usability by reducing the force required to administer a high number of units per injection.

It should be noted that the accuracy and injection force experiments were performed in a laboratory environment, and doses were not delivered into tissue. Although all pens were tested under the same conditions and potential errors minimized where possible, a study investigating the use of the Gla-300 SoloSTAR pen by people with diabetes in clinical practice would be of interest.

Conclusions

The adapted Gla-300 SoloSTAR pen met the ISO acceptance criteria (DIN EN ISO 11608-1:2012)[19] for accuracy at ambient temperature, with the greatest reproducibility between doses and the lowest injection force compared with FlexPen and KwikPen. Such accuracy is encouraging, especially with a lower volume of Gla-300 dispensed for a given dose level versus the insulins dispensed with the other 2 pens. In addition, improved usability through reduced injection force is important for insulin delivery devices, so the lower force needed to inject Gla-300 may have positive implications for diabetes management.

Abbreviations

CV, coefficient of variation; Gla-300, insulin glargine 300 U/mL; Gla-100, insulin glargine 100 U/mL; HMD, half-maximal dose; MD, maximal dose; ISO, International Organization for Standardization.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: David Klonoff has served on advisory panels for Google, Insuline, Lifecare, Novartis, Roche, Sanofi, Tempramed, and Voluntis, has received research support from Eli Lilly, Halozyme, Janssen, and Novo Nordisk, and owns stocks/shares in Tempramed. Irina Nayberg has received honoraria for consultancy from Novo Nordisk. Mona Abdel-Tawab received financial support from Sanofi for carrying out the dose accuracy study. Thomas Haak has served on advisory panels for Merck Sharp & Dohme, Sanofi, Roche, and Emperra, has received consultancy fees from Boehringer Ingelheim, and has received research support from Sanofi, Nintamed, Eli Lilly, and Berlin Chemie AG. Marissa Thonius, Florian See, and Frank Erbstein are employees of Sanofi.

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