Dose Accuracy and Injection Force of Different Insulin Glargine Pens

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Abstract

Background:

Dose accuracy and injection force, representing key parameters of insulin pens, were determined for three pens delivering insulin glargine-based copies, Pen Royale (WR) and DispoPen (WD) for Glaritus® (Wockhardt) and GanLee Pen (GL) for Basalin® (Gan & Lee), compared with pens of the originator, ClikSTAR® (CS) and SoloSTAR® (SS) for Lantus® (Sanofi).

Methods:

Using the weighing procedure recommended by DIN EN ISO 11608-1:2000, dose accuracy was evaluated based on nonrandomized delivery of low (5 U), mid (30 U), and high (60 U) dosage levels. Injection force was measured by dispensing the maximum dose of insulin (60 U for the GL, WR, and WD; 80 U for the SS and CS) at dose speeds of 6 and 10 U/s.

Results:

All tested pens delivered comparable average doses within the DIN EN ISO 11608-1:2000 limits at all dosage levels. The GL revealed a higher coefficient of variation (CV) at 5 U, and the WR and WD had higher CVs at all dosage levels compared with the CS and SS. Injection force was higher for the WR, WD, and GL compared with the CS and SS at both dose speeds. In contrast to the CS and SS with an end-of-content feature, doses exceeding the remaining insulin could be dialed with the WR, GL, and WD and, apparently, dispensed with the WD.

Conclusions:

All pens fulfilled the dose accuracy requirements defined by DIN EN ISO 11608-1:2000 standards at all three dosage levels, with the WR, WD, and GL showing higher dosage variability and injection force compared with the SS and CS. Thus, the devices that deliver insulin glargine copies show different performance characteristics compared with the originator.

J Diabetes Sci Technol 2013;7(5):1346–1353

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Abbreviations: (CS) ClikSTAR, (CV) coefficient of variation, (GL) GanLee Pen, (SD) standard deviation, (SS) SoloSTAR, (WD) DispoPen, (WR) Pen Royale

Keywords: dosing accuracy, injection force, insulin pens

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For patients with diabetes who self-inject insulin, accurate insulin dosing is a requirement to maintain normal glycemia levels and minimize the risk of hypoglycemia or hyperglycemia. Compared with vial and syringe, insulin pens offer substantial improvements in compliance and flexibility.[1,2] Previous studies generally have verified the accurate dosing of insulin pens,[3–7] although single doses outside the International Organization for Standardization limits (DIN EN ISO 11608-1:2000) have been reported in small-scale studies.[3,5,8] Injection force is also a key element in the design of an insulin pen,[9,10] as lower injection forces are associated with simpler operation, more comfortable use,[11] and less injection-site pain.[8]

Insulin glargine (Lantus®, Sanofi) copies, Glaritus® (Wockhardt) and Basalin® (Gan & Lee), have been introduced in several countries. Copies of biological medicinal products are not directly compared and analyzed against a licensed reference biological product according to comprehensive biosimilar regulations.[12] In the case of the insulin glargine copies, differences have been found in the impurity profiles that result from differences in the production process.[12] Because of these differences in impurities, it has been recommended to investigate their immunological potential to ensure patient safety.[12] In addition to the insulin glargine copies not being identical with the original, the devices used to deliver the copies may also differ from those that deliver the original insulin glargine, resulting in different performance characteristics.

The objective of the current study was to evaluate the dosing accuracy and injection force of two reusable insulin pens [Glaritus Pen Royale (WR; Wockhardt) and GanLee Pen (GL; Gan & Lee)] and one prefilled pen (Glaritus DispoPen [WD; Wockhardt]) that have been introduced for injecting Glaritus and Basalin and to compare them with the reusable Lantus ClikSTAR® (CS; Sanofi) and the prefilled Lantus SoloSTAR® (SS; Sanofi) pens. Both reusable and disposable pens combine an insulin vial and a syringe. However disposable pens are prefilled with an insulin cartridge and are discarded when the insulin runs out, whereas reusable pens may be reloaded with insulin cartridges by the user. The pens listed above represent all insulin glargine pens commercially available at the time of the study.

Methods

Study Design

The CS and SS were supplied by the manufacturer (Sanofi, Germany). The other pens were purchased by Sanofi from official pharmacies: GL in China and WD and WR in India. All needles were purchased in Germany by Sanofi. For dose accuracy measurements, all pens were equipped with BD Micro-Fine + 0.25 mm (31 G) × 8 mm needles, and for injection force measurements with BD Micro-Fine + 0.25 mm (31G) × 5 mm needles to ensure comparability of the data. An overview on the pens included in the study is given in **Table 1**.

Table 1.
Insulin Pens Included in the Study

Insulin pen	Manufacturer	Insulin	Dose accuracy	Injection force
			Pen lot	Pen lot
CS	Sanofi	Lantus	C016	C006[a]
WR	Wockhardt	Glaritus	XJ10395	XK11050
GL	Gan & Lee	Basalin	101002-09 01B	XLB01A
SS	Sanofi	Lantus	40 U142[a] 40 U144[a]	C002[a]
WD	Wockhardt	Glaritus	DJi0276	DK11997

[a] The data for these pens have been generated in previous studies.[7,13,14]

For determining dose accuracy, each pen type was tested at a low (5 U), mid (30 U), and high (60 U) dosage level. For the prefilled pens, SS and WD, 15 of each pen type were used to deliver each dosage level, totaling 45 pens for each pen type. For the reusable pens, CS, WR, and GL, all three dosage levels were delivered from one pen using a new insulin cartridge for each dosage level. In total, 15 pens of each reusable pen type were included.

Each dose of the 5, 30, or 60 U dosage levels was dispensed four times in a nonrandomized manner from each pen/cartridge, thus generating 180 values for every pen type (**Figure 1**).[7]

sequence of measurements, two priming doses of 2 U were discarded. If needed, priming was repeated until a drop was seen on the tip of the needle. After delivering each dose and in accordance with the instruction manual for each pen model, the plunger was kept pressed down for 5 s with GL and for 10 s with all other pens to ensure that the entire dose was expelled. Each dose was deposited in a beaker containing a 0.5–1 cm layer of liquid paraffin, while the pen was held close to the surface of the paraffin layer. If an insulin drop remained at the tip of the needle at the end of the relaxation time, this drop was stripped off at the paraffin surface, taking care that the needle did not strike the paraffin. The dose was weighed immediately using an analytical balance (XP205/M, Mettler Toledo AG, Gießen, Germany), which has an accuracy of 0.01 mg. The balance was reset to zero before each dose of insulin was deposited and weighed. The weights were corrected for the specific density corresponding to 1.005 g/cm^3 for Lantus, Glaritus, and Basalin, which had been determined in a preliminary study using a DMA 4500 densitometer (Anton Paar GmbH, Bruchköbel, Germany).

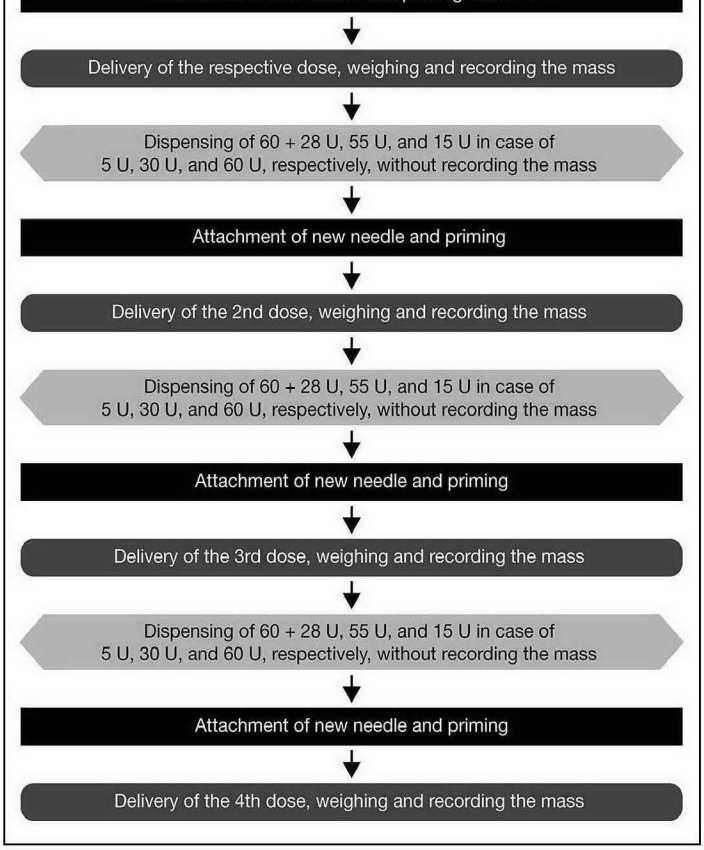

Figure 1. Dose delivery procedure.

The injection forces of the WR and GL reusable pens and the WD prefilled pen were measured in newtons as previously described for CS[13] and SS,[14] using an isometric injection with a Zwick Z0.5 TS testing machine (Zwick GmbH & Co. KG, Ulm, Germany). Prior to the tests, the instrument was calibrated by the manufacturer in a laboratory environment under standard atmospheric conditions. The results obtained for the WR, GL, and WD were compared with previous results generated for the CS[13] and SS.[14]

Twenty pens of each type were tested per test series. Each WR, WD, and GL pen was tested once, whereas each CS pen was tested twice with the same pen[13] and each SS pen three times with the same pen.[14] After priming with 10 U (0.1 ml), the injection force was measured at the maximum dose level for each pen [60 U (0.6 ml) for the WR, WD, and GL; 80 U (0.8 ml) for the CS and SS], applying a constant volume flow rate (injection speed) of 6 or 10 U/s. The comparison of injection forces at constant volume flow rates has been shown to better represent real-life situations.[14]

Preliminary studies were conducted to determine button speeds (millimeters/second) for specific volume flow rates (units/second). The units/second was calculated from the dispensed volume (unit) and the injection time (second). The weight of the dispensed dose was measured using an OHaus Discovery DV 215 CD precision and analytical balance (capacity 210 g; repeatability 0.1 mg, linearity ± 0.2 mg). The conversion into units was done using the density and the concentration (100 U/ml) of the insulin solution. The injection time for complete injection of the dose was calculated from the initial movement of the dose button to an injection force exceeding 2 N per 0.025 s.

Calculated regression lines of volume flow rate versus button speed were used to determine the button speed required for each pen type to achieve a constant volume flow rate of 6 or 10 U/s. For each pen tested, injection forces throughout dose delivery were measured; the maximum injection force was noted and the mean plateau injection force calculated.

The evaluation of dose accuracy was based on the recommendation of the International Organization for Standardization (DIN EN ISO 11608-1:2000).[15] According to DIN EN ISO 11608-1:2000, the acceptance limit for each individual dose should not deviate by more than 1 U for doses < 20 U and not more than 5% for doses >20 U. Hence the acceptance limits for the individual doses tested in this study are 5 ± 1 U (4.0–6.0 U), 30 ± 1.5 U (28.5–31.5 U), and 60 ± 3 U (57.0–63.0 U). In addition, the statistical tolerance interval (95% confidence level) for the whole injection population at each dosage level was calculated according to DIN EN ISO 11608-1:2000, using the formula $\bar{x} \pm [k\ s]$, where $\bar{x}$ is the average dose for the whole population of each pen at each dosage level, s is the corresponding standard deviation (SD), and k is the statistical tolerance limit factor. For $n = 60$, $k = 2.670$ at the 95% confidence interval.[15] The statistical tolerance interval should lie within the upper and lower acceptance limits for each dosage level. The average actual dose, SD, and coefficient of variation (CV) were also determined for each dosage level.

An analysis of variance was used to compare the mean injection forces of the WR, WD, and GL. The significance level was set to 5% ($p = .05$). The mean injection force was also compared with the CS and SS using mean injection force and SD values for the CS and SS from previously published results.[13,14]

Results and Discussion

The present study evaluated the dose accuracy and injection force of the insulin pens manufactured by Wockhardt (WR and WD) and Gan & Lee (GL) for the delivery of the insulin glargine (Lantus) copies, Glaritus and Basalin, and compared them with the reusable CS and prefilled SS pens manufactured by Sanofi to deliver Lantus.

Dose Accuracy

All tested insulin pens at all dosage levels delivered comparable average doses within the range of the DIN EN ISO 11608-1:2000 limits (**Table 2**). The data for the dosing accuracy of the SS have been generated in a previous study using two SS batches. However, this had no negative impact based on the good precision of the SS compared with the other pens, reflecting one single batch. One of the WR pens, being unable to deliver any of the required doses, was found to be faulty and was not included in the evaluation of the dosing accuracy of the WR. At all three dosage levels, the average doses delivered by all pens were lower than the target dose, except for the GL at 5 U, where the delivered dose was greater than the target dose. The WR and WD pens had higher CVs, reaching 6.4% and 5.4% at the 5 U dosage level and ranging between 1.4% and 1.8% at the other dosage levels, respectively. In contrast, both CS and SS had CVs of 2.4% and 3.1% at 5 U, respectively, and did not exceed 0.9% at 30 and 60 U. The dosage variability of the GL with CVs of 3.5% at 5 U and 0.9% at the other dosage levels was intermediate between the CS/SS and WD/WR pens at the 5 and 60 U dosage level and comparable with the SS at the 30 U dosage level.

The distribution of the individual doses according to pen type at the different dosage levels is illustrated in **Figure 2**. The WR and WD pens revealed lower minimum and higher maximum values for the delivered doses at all dosage levels, indicating a greater distribution range compared with the GL, CS, and SS pens.

The calculated statistical DIN EN ISO 11608-1:2000 tolerance intervals were within the acceptance range for the GL, WR, CS, and SS injector populations at all three tested dosage levels (**Table 3**). The WD injector population met the statistical tolerance limits at 5 and 60 U but failed to meet them for dosing accuracy at the 30 U level, as the statistical tolerance interval was less (28.32 U) than the lower acceptance limit at that dosage level (28.5 U). Thus, while the individual 30 U doses with the WD were within the acceptance limit (30 ± 1.5 U) according to DIN EN ISO 11608-1:2000, the whole population failed to meet the statistical tolerance limit, because the variability of the delivered doses was high.

Injection Force

Higher mean plateau and maximum injection forces at 6 and 10 U/s were determined for the GL, WD, and WR at 60 U compared with the CS and SS at 80 U (**Figure 3**). At 6 U/s (**Figure 3A**), the mean plateau injection forces for

Average Actual Doses, Standard Deviation, Coefficient of Variation, Average Deviations, Average Relative Deviations, Absolute Average Deviations, and Average Absolute Deviation From the Target Dose of the Tested Insulin Pens

Pen	Target dose (U)	Actual dose (U)			Average deviation (U)	Average relative deviation (%)	Average absolute deviation[a] (U)	Average absolute deviation[a] (%)
		Average	SD	CV%				
CS	5	4.88	0.12	2.4	-0.12	-2.30	0.13	2.59
Glaritus WR		4.92	0.32	6.4	-0.08	-1.62	0.26	5.28
GL		5.16	0.18	3.5	0.16	3.15	0.20	4.05
SS[b]		4.94	0.15	3.1	-0.06	-1.14	0.13	2.65
Glaritus WD		4.81	0.26	5.4	-0.19	-3.82	0.26	5.28
CS	30	29.53	0.28	0.9	-0.48	-1.60	0.49	1.64
Glaritus WR		29.97	0.54	1.8	-0.04	-0.13	0.42	1.40
GL		29.83	0.26	0.9	-0.18	-0.60	0.25	0.83
SS[b]		29.77	0.25	0.8	-0.23	-0.77	0.28	0.92
Glaritus WD		29.68	0.50	1.7	-0.33	-1.10	0.51	1.68
CS	60	59.19	0.35	0.6	-0.82	-1.36	0.82	1.36
Glaritus WR		59.85	0.81	1.4	-0.15	-0.25	0.65	1.09
GL		59.68	0.52	0.9	-0.32	0.54	0.54	0.90
SS[b]		59.28	0.36	0.6	-0.72	-1.19	0.72	1.19
Glaritus WD		59.59	0.86	1.4	-0.41	-0.68	0.80	1.34

[a] The absolute average deviation reflects the average of the individual absolute values without considering the algebraic signs in units and expressed as percentage of the target dose.
[b] Data for these pens have been generated in a previous study.[7]

Table 3.
Overview of the Statistical Tolerance Intervals Determined for Each Insulin Pen at Each Dosage Level[a]

Units	Actual ISO requirement		Acceptance criteria	CS	WR	GL	SS[b]	WD
5	L	4.0	$\bar{x} - (k\ s) \geq L$	4.58	4.07	4.68	4.54	4.12
	U	6.0	$\bar{x} + (k\ s) \leq U$	5.19	5.77	5.64	5.35	5.50
30	L	28.5	$\bar{x} - (k\ s) \geq L$	28.78	28.51	29.13	29.10	28.32
	U	31.5	$\bar{x} + (k\ s) \leq U$	30.26	31.41	30.51	30.44	31.02
60	L	57.0	$\bar{x} - (k\ s) \geq L$	58.24	57.68	58.31	58.34	57.30
	U	63.0	$\bar{x} + (k\ s) \leq U$	60.13	62.01	61.05	60.23	61.88

[a] ISO, International Organization for Standardization; L, lower limit; U, upper limit.
[b] Data for these pens have been generated in a previous study.[7]

the GL, WD, and WR were significantly different from one another ($p < .05$). They were 95%, 68%, and 50% higher compared with the CS, respectively ($p < .05$) and 53%, 33%, and 18% higher compared with the SS, respectively ($p < .05$). In general, the injection force of all pens increased at 10 U/s. At this speed, the mean plateau injection force of GL was significantly greater ($p < .05$) than that of the WD or WR, which were not different from one another. The GL, WD, and WR were 76%, 37%, and 29% higher than the CS, respectively, and 50%, 17%, and 10% higher than the SS ($p < .05$, each), respectively.

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