Closing the loop, squaring the circle: Studies on insulin delivery, glucose monitoring and the artificial pancreas

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Chapter 4

Dosing accuracy of insulin pens versus conventional syringes and vials

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ABSTRACT

Pen injection devices have acquired a pivotal role in insulin delivery, surpassing the use of conventional insulin syringes in many parts of the world. In this review we sought to determine differences in dosing accuracy between insulin pens and conventional syringes and vials, also touching on patient preference. We aggregated relevant literature found by searching the PubMed database, identifying seven relevant articles. There was consensus that pens are more accurate, especially at doses below 5 insulin units (IU). The literature also showed that pens tend to underdose when compared to syringes, but do this with a high degree of consistency. One study assessed influence on glycaemic control, and whereas no significant difference was found with respect to HbA1c, fasting glucose levels decreased significantly more in pen users vs. syringe users (-57±14 vs. 1±13 mg dL⁻¹, P=0.003). The same study demonstrated that pens improved health related quality of life compared to syringes and vials. We conclude that, regarding accuracy, there is sufficient evidence to recommend the use of insulin pens when delivering doses below 5 IU. For insulin doses above 5 IU there is no clear benefit for the pen in terms of accuracy.
INTRODUCTION

Since the start of insulin treatment more than 85 years ago, clinicians and industry have set out to improve the efficacy and accuracy of insulin delivery. Insulin pen injection devices play an important role in increasing patient comfort and reducing the daily burden of diabetes management, and as such they are suggested to increase treatment compliance (1). Starting with the introduction of the NovoPen® (Novo Nordisk A/S, Bagsværd, Denmark) in 1985, a plethora of insulin pens have been introduced (2). Most insulin pens have been designed for ease-of-use, to minimize pain during injection and to conform to a socially accepted design. The importance of ease-of-use of insulin pen injection devices increases with an ageing diabetic population and the decreasing manual dexterity and vision related to this ageing process (3). These factors have led to the wide-spread use of insulin pen injection devices, particularly in Europe where 86% of the total volume of insulin is being injected with a pen injection device (4), this in stark contrast with the United States where in 2002 less than 10% of insulin users administered their insulin with a pen injection device (5), although this is increasing. Even though the majority of patients seem to prefer the use of insulin pen devices, the question remains whether the use of insulin pen injection devices actually increases the dosing accuracy compared to the use of syringes. Limited data exists on this topic. The purpose of this article is to review the literature on differences in accuracy between insulin pen injection devices and syringes/vials.

STUDY DESIGN AND METHODS

A literature search was performed using the PubMed online database (http://www.pubmed.gov) for entries published since 1985 until December 2009. We used a combination of the following search terms; “Insulin” [MeSH] or “Insulin” combined with “Syringes”[MeSH] or “Syringes” or “Pen”, combined with “Precision” or “Accuracy”. We limited our search results to articles in the English language.
From the publications identified, those that met all of the following criteria were selected for inclusion in this review.

1. Comparison of conventional insulin pen injection devices (i.e. no jet devices) with conventional syringes or syringes specifically manufactured for use in insulin administration.
2. Description of accuracy in the form of dosage error or description of ease-of-use in delivery of a set dose of insulin.

We further examined the selected articles to ascertain whether they referenced additional articles relevant to our research question, which had not been found by our search in the PubMed online database.

RESULTS

The initial search resulted in 36 articles, seven of which met the selection criteria (2;6-11). No additional articles were included by means of reference-review. Five of the included articles primarily investigated the accuracy and reproducibility of insulin delivery by pen injection device versus syringes/vials. The other two articles focused primarily on ease-of-use in delivering a set dose and patient preference or confidence in administration of insulin.

**Used Methodologies**

All five studies on dosage accuracy and precision used the methodology of dispensing variable doses from various pen injection devices or syringes/vials (see Table 1). The accuracy of the dispensed dose was then assessed using precision gravimetric methods(6;7;10;11) or scintillation spectroscopy (8). In a study by Gnanalingham et al (6), various insulin doses were dispensed 15 times each from five pen injection devices from two different brands by a single investigator and from 30 IU syringes handled by five nurses. This enabled the investigators to determine the accuracy of insulin delivery devices at previously determined doses. In a study by Lteif et al (8), children with type 1 diabetes and their caretakers (n=24) were asked to measure their regular morning insulin dose three times with either a pen injection device or
Dosing accuracy of pens vs. syringes

regular syringe, using radio-actively labeled insulin. This study allowed investigators to determine accuracy of insulin delivery devices at common pediatric doses, and the real-life accuracy of such devices in the hands of the patient. A study by Keith et al. (7) further assessed accuracy and precision of low-dose insulin administration, and included a pump device for comparison. In this study, three different pen injection devices, two different syringes and an insulin-pump were used. From each device, the relatively low doses of 1, 2 and 5 IU were dispensed 15 times each. Again, to rule out any inter-operator bias, all doses were dispensed by the same investigator. Another investigator performed all scale measurements. A study by Ignaut et al. (10) allowed the patient to set a dose of 5, 30, and 60 IU which were then dispensed by investigators, and compared the accuracy of unspecified syringes with two different pen injection devices. A study by Asakura et al (11) allowed healthcare professionals, both experienced with and naïve to insulin treatment, to administer doses of 10 IU with both conventional syringes and a FlexPen comparing their accuracy.

Results
The data from Gnanalingham et al. showed that syringes consistently delivered more insulin than pen injection devices, especially at 1 IU doses (+34% and +38% compared to NovoPens and BD-pens respectively). The accuracy of the two pen injection devices was similar and the pens were significantly more accurate than syringes, especially at the lower doses of 1, 2, and 5 IU (P <0.0001). The data also showed that reproducibility of actual doses was similar for both pen injection devices and syringes (coefficient of variation < 7%), suggesting that both pen injection devices and syringes were consistent in underdosing or overdosing insulin, respectively. The authors concluded that administering small volumes of insulin is problematic with pen injection devices but even more so with syringes. The study by Lteif et al. showed that the absolute error in measuring out doses <5 IU was greater with syringes than pen injection devices (9.9% ± 2.4 for syringes 4.9% ± 1.6 for pens). When the number of dosed units was >5 IU, more resembling usual adult insulin doses, the measuring errors for insulin syringes and pen injection devices became comparable (3.2% ± 0.6 for syringes, 2.2% ± 0.4 for pens). The authors therefore concluded that pen injection devices are more accurate than insulin syringes, particularly at low doses of insulin, commonly used in the pediatric population.
The study by Asakura et al. only studied the delivery of 10 IU doses and showed that the FlexPen was more accurate at delivering the 10 IU dose versus the syringe both by healthcare professionals (HCP) experienced with insulin injection and healthcare professionals naïve to insulin injection (experienced HCPs: 9.91 ± 0.12 g versus 9.82 ± 0.25 g, P<0.001, for naïve HCPs: 9.91 ± 0.12 g versus 9.74 ± 0.85 g, P<0.001).

Two studies demonstrated superior accuracy of pen injection devices at the lower insulin doses (<5 IU). The study by Keith et al. focused primarily on 1, 2 and 5 Unit doses of insulin. Data from this study again showed that differences in accuracy between devices depended on the size of the target dose; the lower the target dose, the greater percent error. The accuracy of devices within the same category (i.e. pens, pumps or syringes) was statistically similar. For the 1 IU dose, pens provided the greatest accuracy and syringes the least (P<0.001). For the 2 IU dose, the pump and pens performed equally well, while syringes had the lowest accuracy. For the 5 IU dose, all devices performed equally well in all categories. The investigators then examined the precision of the various categories, defining precision as the absolute percent difference from the group sample mean. The data showed that differences in precision were independent of the size of the target dose (P=0.44) and no significant differences in precision were noted within a single category. In particular the devices with ½ IU markings (BD Mini Pen and Precision Sure-Dose Syringes) were not statistically significantly more precise than those with 1 IU markings. The pump was the most precise device (P<0.001). The author’s concluded that the pen injection devices and the pump were the most accurate in administering doses <5 IU and that syringes were highly inaccurate at doses <5 IU.

In a non-inferiority study by Ignaut et al, patients were asked to set insulin doses which were then administered onto a scale by research staff. Their data showed superiority of the pen device at 30 IU (95% confidence interval (CI) 0.0028-0.0186mL with an assumed equivalence margin (EM) of 0.015mL) and 60 IU (95% CI 0.0163-0.0437mL with an assumed EM of 0.03mL), but could not demonstrate any difference between pen injection devices and syringes at 5 IU (95% CI 0.0013-0.0047mL with an assumed EM of 0.01mL). The fact that the difference in accuracy between the pen injection device and conventional syringe after administration of 5 IU was not significant can be attributed to the choice of a relatively high equivalence margin of 0.01 mL (corresponding with 1 IU).
Thus, there seems to be sufficient data to conclude that the accuracy of syringes is inferior especially at lower doses of insulin. Only the study by Ignaut et al. failed to demonstrate superiority of pens at <5 IU, with the methodological issue discussed above. Additionally, a review of literature by Pfützner et al. (2), which included literature that reviewed dose accuracy and patient preference of the FlexPen® compared with syringes or vials, concurred with the conclusion that pen injection devices consistently demonstrate better dose accuracy than syringes and vials.

Diminished accuracy of syringes and vials is particularly worrisome in pediatric settings where due to the frequent use of doses <5 IU, adverse clinical consequences, like hypoglycaemia, can ensue (12). To prevent these adverse clinical consequences Gnanalingham et al. advocate returning to the use of more diluted insulin solutions (i.e. 40U/mL), mostly discontinued in the USA and UK after 1983. Hereby the volume to deliver 1 IU increases, diminishing the consequences of possible inaccuracies.

Keith et al. further encourage caregivers to manually dilute 100U/mL solutions, so that low-dose insulin can be given with more confidence. However, manual dilution carries a risk of dilution errors so the authors conclude that pen or pump devices should be considered as alternatives. For people with very low basal insulin requirements, at dosages where one injection may not cover 24 hours, insulin pump therapy is often a solution.

To take advantage of the superior accuracy, patients need to be educated in pen injection device use and need to be taught to renew the needle before each injection and to perform air shots. Also because of the compressible elements of insulin cartridges used in pen injection devices, insulin is delivered more slowly with a pen injection device, compared to conventional syringes. Patients need to be taught to leave the needle in place subcutaneously after injection for ten seconds to attain optimal delivery of insulin. (13)

**Ease-of-use and patient preference**

Ease-of-use of insulin injection devices and patient compliance to treatment play an important role in maintaining optimal glycaemic control (4). Accuracy of insulin administration is not only a matter of device accuracy, but also of ensuring correct use by the patient. A study of Korytkowski et al. (9) analyzed patient preference
between pen injection devices and conventional syringes and their ease-of-use. 121 patients who were only familiar with the use of syringes/vials were included in the study. Patients started with a 4-week run in period in which they used their own syringes/vials to administer Humalog 70/30. Patients were then randomized to use of a prefilled, disposable pen device for four weeks and then crossed-over to four weeks syringe/vial use, or the reverse sequence. At the end of the study patient preference was measured using a questionnaire. The data showed that 74% of patients indicated a preference for the pen injection device. 20% had a preference for the syringe/vial and 6% had no preference. 82% of patients indicated more confidence with setting the required dose on a pen injection device, versus 11% who where more confident using syringes/vials. 85% of patients also indicated that they felt the dose scale easier to read on the pen injection device in comparison with 10% of patients who felt the dose scale on syringes/vials was more easily read. 73% of patients felt more confident that the pen injection device delivered an accurate dose of insulin, versus 19% for syringes/vials. Finally, 61% of patients felt that with the pen injection device they were more confident in their own ability to maintain glycaemic control, versus 16% for the syringes/vials. The authors conclude that more patients expressed a preference to continue use of the pen injection device, even though efficacy of treatment between pen injection devices and syringes/vials appeared similar. Concurring with the previously discussed study, a review by Molife et al. (14) reported on the outcomes of 29 studies with patient preference as a primary outcome. Of the 29 studies included in their review, 28 studies reported that a majority of patients preferred pen injection devices over syringes/vials, measured as a stated preference or a willingness to continue treatment with a pen injection device rather than with syringes/vials. The one study in which participants did not express a clear preference for pen injection devices found no difference in preference for either pen or syringe. It should be noted however that preference was defined differently across studies. In the same review nine studies which evaluated ease-of-use were presented, all of which showed that the majority of patients found pen injection devices to be easier to use than syringes/vials.
Clinical benefits

The potential of pen injection devices to improve glycaemic control has been shown in a recent study by Lee et al. (15) in which half of a group of type 1 and 2 diabetes patients who used syringes switched to insulin pen injection devices. Fasting glucose decreased significantly in the insulin pen group (-57±14 mg dL$^{-1}$, $P<0.001$) and the reduction in fasting glucose levels was significantly greater than a reduction that occurred in the group still using syringes (-57±14 vs. 1±13 mg dL$^{-1}$, $P=0.003$). However, HbA1c levels were not significantly decreased in comparison with baseline in both groups. The authors concluded that the use of insulin pen injectors improved glycaemic control. The study also measured health related quality of life (hrQoL) by means of a questionnaire (SF-36), and showed that hrQoL improved in the group using the pen injection device. with advantages of the insulin pen more obvious in physical terms than in mental terms in the SF-36 questionnaire. Noting that a patient’s feeling of well-being might not be reflected in their metabolic status; indeed the study could not demonstrate any relation between the reduction of fasting glucose and improvement in hrQoL.
**Table 1. Overview of Study Designs**

<table>
<thead>
<tr>
<th></th>
<th>Gnanalingham et al.10</th>
<th>Lteif and Swenck8</th>
<th>Keith et al.7</th>
<th>Asakura et al.11</th>
<th>Ignaut et al.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses delivered (IU)</td>
<td>1, 2, 5, 10</td>
<td>Regular morning</td>
<td>1, 2, 5</td>
<td>10</td>
<td>5, 30, 60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dose of patient</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Means of</td>
<td>Gravimetric</td>
<td>Scintillation</td>
<td>Gravimetric</td>
<td>Gravimetric</td>
<td>Gravimetric</td>
</tr>
<tr>
<td>accuracy assessment</td>
<td></td>
<td>spectroscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pens investigated</td>
<td>NovoPen 1.5 BD pen</td>
<td>Patient’s personal pen, including NovoPen 1.5 and Autopen</td>
<td>Humalog pen NovoPen BD Mini pen</td>
<td>FlexPen</td>
<td>FlexPen KwikPen*</td>
</tr>
<tr>
<td>Syringes used</td>
<td>BD Micro-Fine 30U</td>
<td>BD U100 0.3 mL BD U100 0.5 mL Terumo U100 0.25 mL</td>
<td>BD Ultra-Fine II Short Needle 30 U Precision Sure-Dose 30 U</td>
<td>BD LoDose syringes 30-gauge 8-mm needles</td>
<td>Not specified</td>
</tr>
<tr>
<td>Pump used</td>
<td>NA</td>
<td>NA</td>
<td>H-TRON Plus V100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Person delivering</td>
<td>Various investigators</td>
<td>Patient or caregiver of patient</td>
<td>Single investigator</td>
<td>Hospital care professionals, both experienced and insulin-naive</td>
<td>Patient set dose, investigators delivered</td>
</tr>
<tr>
<td>dose</td>
<td></td>
<td></td>
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</tbody>
</table>

NovoPen and FlexPen are manufactured by Novo Nordisk A/S (Bagsværd, Denmark), BD materials by Becton Dickinson (Franklin Lakes, NJ), Humalog and KwikPen by Eli Lilly and Co. (Indianapolis, IN), Autopen by Owen Mumford Ltd. (Woodstock, United Kingdom).

**CONCLUSION**

The accuracy of devices used for insulin administration is an important issue. Patients rely heavily upon device accuracy to administer the correct amount of insulin. Errors in the insulin dose administered can lead to diminished glycaemic control and hypoglycaemia. The literature reviewed in this article shows consensus regarding the increased accuracy of pen injection devices, particularly at doses <5 IU. This increased accuracy is not only evident when the devices are used by patients themselves, but also when the devices are used by a single investigator or medical personnel. Patients have a preference for pen devices over the use of syringes, and
find that pen devices are easier to use and increase confidence in their ability to maintain glycaemic control. Patients also experience improved quality of life with the use of a pen injection device compared to the use of syringes. We conclude that, regarding accuracy, current review findings support the use of pen injection devices versus syringes/vials, particularly when prescribing doses of <5 IU. For insulin doses above 5 IU there is no clear benefit for the pen in terms of accuracy.
REFERENCE LIST


