Accuracy of Pen Injectors Versus Insulin Syringes in Children With Type 1 Diabetes

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OBJECTIVE — To compare the accuracy and precision of insulin syringes and pen devices used by children with type 1 diabetes and their parents.

RESEARCH DESIGN AND METHODS — There were 48 subjects (32 patients, a parent of an additional 16 patients) instructed to measure out morning insulin doses three times from vials and/or cartridges containing saline mixed with small amounts of [^{14}C]glucose (solution used as regular insulin) and [^{3}H]glucose (solution used as NPH insulin) and to dispense the contents into a scintillation vial. Statistical analysis was used to determine the accuracy and precision of both methods of insulin delivery.

RESULTS — The absolute error in measuring out doses of regular insulin <5 U was greater with insulin syringes compared with pen injection devices (9.9 ± 2.4 vs. 4.9 ± 1.6%, respectively). Both were comparable for regular insulin doses >5 U (3.2 ± 0.6 vs. 2.2 ± 0.4% for syringes and pens, respectively). The accuracy in drawing up NPH doses was similar for low and high insulin doses (mean percent error of 7.5 ± 1.5 vs. 5.6 ± 1.1%).

CONCLUSIONS — Pen devices are more accurate than insulin syringes in measuring out insulin at low insulin doses. The accuracy of insulin syringes improves when higher doses of regular insulin are measured out and becomes comparable to pen devices.

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Insulin is most commonly delivered to children with type 1 diabetes via pen injection devices and insulin syringes. Little data exist concerning the accuracy and precision of these two methods of insulin delivery in children. Whereas several studies have compared glycosylated hemoglobin levels (a measurement of diabetes control) in patients using a pen versus a syringe (1–5), we are not aware of any study comparing the accuracy of these two insulin delivery systems in children. The aim of this study was to compare the accuracy and precision of insulin syringes and pen devices in children. We hypothesized that low insulin doses would be measured less accurately than high insulin doses and that a pen device may be more accurate in delivering insulin than an insulin syringe. We also aimed to determine how frequently contamination of NPH by regular insulin occurs when children and caregivers are drawing an insulin mixture and whether any correlation exists between an individual's frequency of hypoglycemic events and the accuracy and precision of insulin measurement by the patient or caregiver.

RESEARCH DESIGN AND METHODS

Subjects

A total of 48 subjects, including 32 children with type 1 diabetes and a parent of an additional 16 children with type 1 diabetes, were recruited during a routine follow-up at the Mayo pediatric outpatient diabetes clinic. Twenty-four children and adolescents (mean age of 14.1 years) were on the multiple daily injection (MDI) program (one injection of regular insulin before each meal and ultralente at supper or bedtime) and knew how to use both pen injectors and insulin syringes. There were 24 children (mean age 9.8 years) on the mixed-split regimen (two doses of regular and NPH mixed) who required the mixing of regular and NPH and the use of insulin syringes.

Experimental methods

Vials and/or cartridges were filled with a ^{14}C-radiolabeled solution by adding 0.0007 µCi of [^{14}C]glucose to 0.25 cm^3 of a saline solution. These were substituted for regular insulin. In addition, vials were filled with a ^{3}H-radiolabeled solution by adding 0.001 µCi of [^{3}H]glucose to 0.25 cm^3 of a saline solution. These were substituted for NPH insulin. Each drawn sample contained a maximum of 1,000 cpm. For each participant, the amount of ^{14}C and ^{3}H present in each vial or cartridge was determined independently by A.N.L. ^{3}H and ^{14}C concentrations were measured by using a transfer pipette (Pipetman; Rainin, Woburn, MA). The coefficient of error of these standard procedures was 1%. Dual counting of ^{14}C and ^{3}H (with background subtraction) was performed by scintillation spectroscopy using a Wallac liquid scintillation counter.

Procedures

Under supervision, subjects were instructed to measure out morning insulin doses three times from vials and/or cartridges containing saline mixed with small amounts of [^{14}C]glucose (solution used as regular insulin) and [^{3}H]glucose (solution used as NPH insulin). For 16 of the 24 children on the mixed-split program, the child's caregiver rather than the child was asked to draw up the insulin doses, because the caregiver was routinely administering the insulin doses. Children or caregivers with hand cuts or vision impairment and those who had an insulin dose that routinely exceeded 25 U were excluded. Subjects regularly using a pen device (n = 24) were

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Abbreviations: CV, coefficient of variation; MDI, multiple daily injection.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

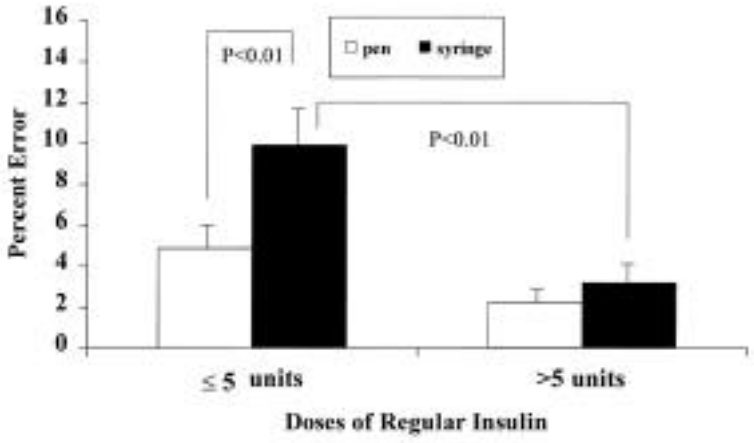

Figure 1—*Accuracy of pen injection devices vs. insulin syringes. The accuracy of both methods of delivery was similar for insulin doses ≥5 U (*n *= 15, or 45 observations). Pen injectors were more accurate than syringes for doses <5 U (*n *= 9, or 27 observations).*

asked to make measurements of regular insulin using both the pen and the syringes. Subjects using an insulin mixture withdrew the dose of regular insulin first and then the dose of NPH. The content of the drawn up samples was then dispensed into scintillation vials. The NPH solution containing ^{3}H was sampled to determine the amount of ^{14}C contamination.

Becton Dickinson U100 syringes (0.3- and 0.5-ml syringes; Becton Dickinson, Franklin Lakes, NJ), Terumo U100 syringes (0.25 ml in one-half U increments; Terumo, Somerset, NJ), and pen devices, including Novopen 1.5 (Novo Nordisk Pharmaceuticals, Princeton, NJ) and Autopen (Owen Mumford, Marietta, GA), were used to exactly match the home procedure.

For each child, glycosylated hemoglobin levels were recorded at the time of the clinic visit. In addition, average blood glucose concentration and percentage of low blood glucose measurements in the preceding 250 tests recorded in the patient's One Touch glucose meter (LifeScan, Milpitas, CA) were determined using the One Touch diabetes data management program.

Definitions

$$\text{Accuracy (\% error)} = \frac{\text{expected insulin dose} - \text{actual insulin dose} \times 100}{\text{expected insulin dose}}$$

$$\text{Coefficient of variation (CV)} = \frac{\text{SD} \times 100}{\text{mean insulin dose}}$$

Low blood glucose (hypoglycemia) = blood glucose measurement that is below the goal range for each individual patient (<70 mg/dl in our patients).

Statistical analysis

Data were expressed as means ± SE when applicable. Student's *t* test was used for the comparison of continuous variables. Fisher's exact test was used for categorical variables. Pearson's correlation test and the straight multiple regression analysis were conducted to examine the relationship between selected variables. $P < 0.05$ was considered significant.

RESULTS

Accuracy of pen injectors compared with insulin syringes

We compared the accuracy of pen injectors with insulin syringes using the 24 subjects on the MDI program. For insulin doses ≤5 U (*n* = 9, 27 observations), the absolute error in measuring out regular insulin via pen devices (mean insulin dose of 4.1 ± 0.4 U) was less than the absolute error in measuring out regular insulin via insulin syringes ($P < 0.01$). However, both devices were comparable for regular insulin doses >5 U (*n* = 15, 45 observations) (Fig. 1).

Dose-dependent accuracy of regular insulin

In subjects using both syringes and pen devices (*n* = 24), the accuracy of pen injectors improved slightly but not significantly for insulin doses >5 U (Fig. 1). However, syringes delivered insulin doses >5 U more accurately than insulin doses ≤5 U (Fig. 1). In terms of actual units, the absolute error in measuring out insulin was similar for low and high doses of insulin whether using the pen or the syringe. The errors in pen measurements were 0.2 ± 0.05 and 0.27 ± 0.06 U for insulin doses ≤5 and >5 U, respectively, while the errors in syringe measurements were 0.4 ± 0.1 and 0.4 ± 0.07 U for insulin doses ≤5 and >5 U, respectively. Participants on the mixed-split regimen also drew up regular insulin doses ≤5 U less accurately (mean percent error 13.4 ± 3.7 vs. 2 ± 0.6% for doses ≤5 and >5 U, respectively) (Fig. 2). Comparing the dose-dependent accuracy of regular insulin in all subjects (*n* = 48), we also found that insulin doses ≤5 U (mean insulin dose of 3 ± 0.3 U) were measured out by syringes less accurately than insulin doses >5 U (mean insulin dose of 11.1 ± 0.8 U). All subjects included, the mean percent error in measuring out regular insulin via a syringe was 12.3 ± 2.6 vs. 2.9

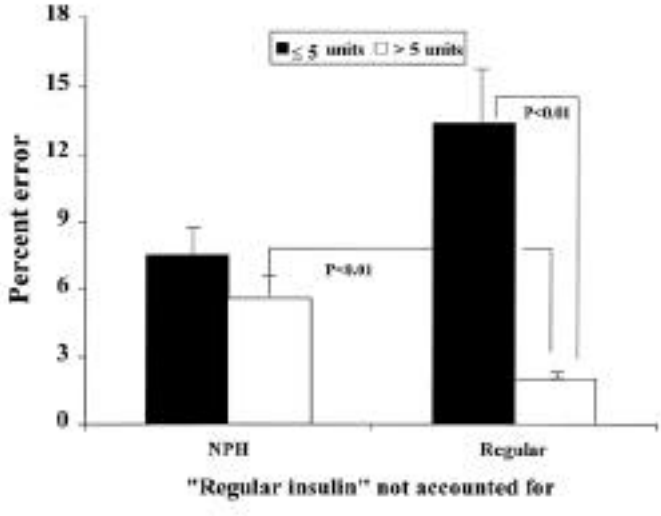

Figure 2—*Accuracy of NPH measurements (error in regular insulin not taken into consideration). The accuracy in drawing up NPH was similar for low (*n *= 15, or 45 observations) and high (*n *= 9, or 27 observations) insulin doses. For doses ≤5 U, regular insulin was measured out less accurately than was NPH.*

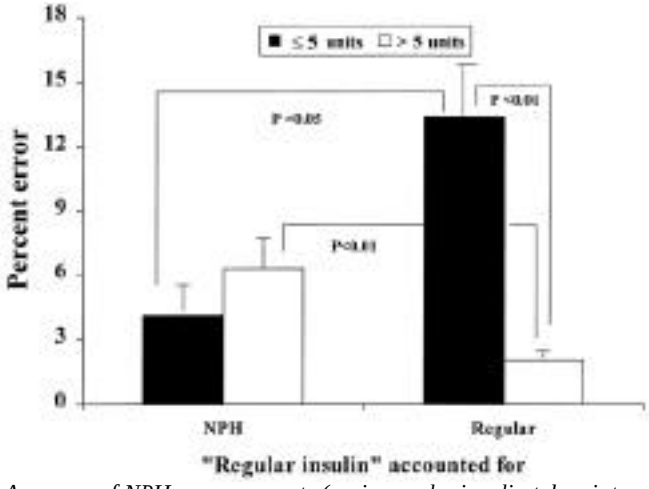

Figure 3—*Accuracy of NPH measurements (error in regular insulin taken into consideration). The accuracy in drawing up NPH was similar for low (n = 15) and high (n = 9) insulin doses. For doses >5 U, regular insulin was measured out more accurately than was NPH.*

± 0.5% for insulin doses ≤5 and >5 U, respectively.

Dose-dependent accuracy of NPH

All 24 participants on the mixed-split program were included. The accuracy in measuring out NPH was similar for low (n = 15, 45 observations) and high (n = 9, 27 observations) insulin doses (Fig. 2). When the error in measuring out regular insulin (which is drawn up first) was taken into consideration, NPH was measured out more accurately than regular insulin for doses ≤5 U ($P < 0.05$) and less accurately for doses >5 U ($P < 0.01$) (Fig. 3).

Children compared with caregivers

All subjects using the pen devices were children and adolescents with diabetes. Therefore, the accuracy of caregivers was compared with the accuracy of children only when an insulin mixture was used, and for regular insulin doses ≤5 U. Children with diabetes (n = 5) were as accurate as their parents (n = 14) in measuring out the insulin dose (mean percent error of 14.5 ± 5.4 vs. 11.6 ± 4.2% for children and parents, respectively).

Contamination

Only one patient contaminated the NPH vial with regular insulin during one of the three measurements. We detected 8% of the total amount of regular insulin that was drawn in the NPH vial.

Precision of insulin measurements

In subjects using both systems (n = 24), the mean CV was 3.2% for pen injectors and 3.8% for syringes. In this group, the dose reproducibility was better when insulin doses >5 U were measured out. Pen injectors had a CV of 4.7 ± 1 vs. 2.4 ± 0.4% for insulin doses ≤5 and >5 U, respectively ($P < 0.05$), while insulin syringes had a CV of 5.3 ± 1.3 vs. 2.9 ± 0.4% for these same doses ($P < 0.05$).

Correlation between hypoglycemic events and percent error

Regardless of insulin program, patients were asked to test blood glucose four to five times daily. Computer analysis of reflectance glucose determinations was available in 41 patients. The average number of tests stored in the computer's memory was four tests per day. When using an empirical cutoff for frequency of low blood glucose measurements of 20% (of total blood glucose tests in the meter), 10 of 11 children with lows that exceeded 20% measured out more regular insulin than expected (positive percent error). However, only 15 of 30 children with lows that did not exceed 20% drew up more regular insulin than expected ($P < 0.05$). There was a positive correlation between percent lows and accuracy of regular insulin doses (r = 0.4, $P < 0.01$). A positive correlation was also present between percent lows and error in terms of actual units of regular insulin (r = 0.4, $P < 0.01$). However, both these correlations were not significant when corrected for insulin dosage and age as potential confounding variables.

CONCLUSIONS — The accuracy and precision of insulin delivery to children with diabetes have rarely been assessed in clinical practice. Weighing insulin doses and γ-counting are the two techniques that have been used for that purpose (6–11). In a previous study, two disposable insulin injection devices (NovolinPen and NovolinSet; Novo Nordisk Pharmaceuticals) (12) gave a remarkable degree of accuracy. To our knowledge, no one has previously compared the accuracy of pen injectors with the accuracy of insulin syringes in the hands of children with type 1 diabetes or their caregivers.

We found that pen injectors are more accurate than syringes when low doses of insulin are measured out. For doses >5 U, these two insulin delivery systems were comparable. The lowest dose of insulin measured out by a pen device was 2 U. Therefore, it seems that there is a clear advantage in using pen devices for insulin doses between 2 and 5 U. For insulin doses that exceed 5 U, patients may choose either delivery system and have similar results.

Note that in this study, saline with added ^{14}C and ^{3}H was used for insulin because of cost. We cannot rule out the possibility that if actual insulin solution had been used, our results might have been different. For example, a protein-containing solution may affect the development of air bubbles. However, we do not feel that our overall results would be changed, since the same solution was used for both the pen injection devices and the insulin syringes.

Inaccuracies were found when two insulins were mixed in the syringe before injection (10,11). Errors were most significant with low insulin doses (8,9,13). Previous studies have shown that parents and pediatric nurses made large errors in drawing up insulin doses <2 U, and that caregivers of children with diabetes receiving low insulin doses delivered amounts greater than intended (7,8). Our study is consistent with these results only for regular insulin (in the mixed-split program), which is drawn up first. Syringes were similarly accurate for insulin doses of NPH, whether they were <5 or >5 U. Therefore, we speculate that the greater inaccuracy in delivering low doses of regular insulin is due in part to the presence of a small dead space and to technical problems with air bubbles, which might be expected to have a greater effect on the insulin that is drawn up first.

Dose reproducibility with pen injectors was 3.2% and was comparable to a reported dose reproducibility of 2% when new Novopen injectors were used (6).

Dose reproducibility with syringes in the same subject group was 3.8%. Dose reproducibility was better for insulin doses >5 U compared with doses <5 U. Therefore, we conclude that low doses of insulin are measured out with greater variability when both pen injector devices and insulin syringes are used. For the same insulin doses, pen injectors and syringes are similarly reproducible.

Children (mean age of 11.5) were as accurate as their parents in measuring out an insulin dose. In addition, reported mean percent error of older patients (14) using the syringe is similar to the mean percent error of children and adolescents who drew up doses >5 U. Therefore, we feel that younger patients with type 1 diabetes can be allowed to draw up and administer their own dose of insulin.

It has been suggested that the higher rate of hypoglycemia in young children may be due to the increased percent error in giving small amounts of insulin (13). We found that there was a simple correlation between percent error, as well as actual error, and frequency of hypoglycemia. When corrected for insulin dosage and age as potential confounding variables, these correlations lost their significance.

One can only speculate on the clinical significance of this data. A large randomized study in children on relatively low doses of insulin using the insulin pen or syringes would be needed to fully address this issue. The improved accuracy of measuring out insulin with the pen device, however, might help minimize one of the variables affecting blood glucose concentrations.

We conclude that pen injectors are accurate systems of insulin delivery. Their use should be encouraged when low doses of insulin are being administered. The accuracy of insulin syringes improves and becomes comparable to pen injector devices when higher doses of regular insulin are administered.

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