# Insulin pen for administration of isophane insulin

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## Abstract

**This study was made in order to evaluate the acceptability and convenience of using the NovoPen™ with NPH-insulin (Protaphane HM™) and to investigate whether NPH-insulin was properly suspended when used in the NovoPen. Forty patients with insulin-dependent diabetes mellitus, all on multiple injection therapy, were randomly allocated to one of two treatment groups starting with either the NovoPen or conventional syringes for their injections of NPH-insulin as basal insulin. No differences were found between the groups in $HbA_{1c}$, blood glucose profiles, total insulin dosage or number of hypoglycaemic events. When the NovoPen with NPH-insulin was used total soluble insulin doses were significantly higher (31.3 vs 29.9 U/day, p = 0.02) as was the pre-breakfast dose (11.1 vs 10.6 U/day, p = 0.04). Out of 40 patients 39 were confident of achieving dose accuracy, 39 found it easy to resuspend NPH-insulin in Penfill™ (insulin cartridge for the NovoPen) and 38 chose to continue using the NovoPen for basal insulin when the study was finished. The conclusion is that the NovoPen is a safe, convenient and acceptable device for administering NPH-insulin.**

*Key words: NovoPen, NPH-insulin, basal/bolus, syringes*

## Introduction

The NovoPen™ (an insulin injection pen with cartridged insulin) has been invented to facilitate and simplify the injection of soluble insulin (Actrapid HM™), primarily for patients on multiple injection therapy, as an alternative to conventional syringes and needles. Several studies show that the NovoPen is reliable and safe and that accuracy of dose has been achieved. The NovoPen has also proved to be a convenient and acceptable means of administering multiple injection therapy *(Refs 1-9)*.

These studies referred to were all concerned with the administration of soluble insulin using the NovoPen. So far only few studies have been published where the NovoPen has been used for administration of intermediate acting insulin *(Refs 10-16)*.

NPH-insulin has to be resuspended before injection, which is easily done when this insulin is in vials as they contain some air. Since Penfill™ (the insulin cartridge for the NovoPen) contains no air the technical problem of ensuring correct resuspension before injection has been solved by adding a tiny glass ball to the Penfill.

The aims of this study were to evaluate the acceptability and convenience of the NovoPen using NPH-insulin in Penfill and to investigate whether NPH-insulin (Protaphane HM™) can be given safely when used in Penfill.

## Patients and methods

Forty patients with insulin-dependent diabetes mellitus participated in the study. They were all accustomed to measuring and monitoring the blood glucose at home and trained to adjust their insulin doses on the basis of their blood glucose values. All were treated with multiple injection therapy with three or four meal-related injections of soluble insulin in an insulin pen and with NPH-insulin in vials as basal insulin. Baseline data for the patients are shown in *Table 1*.

The study was a randomized cross-over study with two treatment periods of 12 weeks each. The patients were randomly allocated to one of two treatment groups. One group with 20 patients in the first treatment period used the NovoPen/Penfill and in the second treatment period conventional syringes for their injections of NPH-insulin. The other group also consisted of 20 patients who used conventional syringes in the first treatment period and the NovoPen/Penfill in the second treatment period for their injections of NPH-insulin. Both groups continued to take their meal-related injection of soluble insulin with the NovoPen/Penfill.

Outpatient visits took place at 0, 6, 12, 18 and 24 weeks during the study period. On each visit records were made of the following using a structured protocol: state of injection sites, injection technique, technical problems with the NovoPen, adverse reactions, patient complaints and number of hypoglycaemic reactions during the preceding week. The hypoglycaemic reactions were graded on a three-graded scale defined as follows: Grade 1 — tremor before meals but no action taken; Grade 2 — sweating, dizziness or blurred vision responding within ten minutes to a biscuit or meal; Grade 3 — reduction in level of consciousness requiring assistance of another person. On all visits $HbA_{1c}$, weight and insulin doses were registered. Before each visit each patient recorded — at timepoints 0, 12 and 24

***Table 1***
*Baseline patient data*

| | | Pen | Syringe |
|---|---|---|---|
| Number | | 20 | 20 |
| Age (y) | | 36.4 | 34.4 |
| Duration of diabetes (y) | | 17.0 | 10.8 |
| Blood pressure | — systolic (mmHg) | 132 | 123 |
| | — diastolic (mmHg) | 82 | 78 |
| Dose insulin | — soluble (U/day) | 32.2 | 28.8 |
| | — NPH (U/day) | 17.2 | 17.3 |
| Total dose insulin (U/day) | | 0.72 | 0.63 |
| Retinopathy | — none | 8 | 14 |
| | — simple | 6 | 3 |
| | — proliferative | 6 | 3 |
| Proteinuria | — none | 16 | 18 |
| | — intermittent | 2 | 1 |
| | — persistent | 2 | 1 |

*This table shows baseline data for patients in the two groups starting with either pen or syringes. No significant differences were detected.*

weeks — a 7-point blood glucose profile using strips (BM-Test Glycaemi 1-44, Boehringer Mannheim, Mannheim, FRG).

At the end of the study acceptability and convenience were evaluated by means of a questionnaire.

Chi-square analyses, Student's two-sample t-test and analyses of variance were performed for statistical evaluation of differences between groups. A p-value $\leq 0.05$ was considered as significant.

## Results

At baseline no differences were found between the two treatment groups *(Table 1, previous page)*. There were no drop-outs.

No significant differences were found when the two study periods were compared with regard to $HbA_{1c}$, total daily insulin doses or number or grade of hypoglycaemic events *(Table 2* and *Figure 1)*.

The seven-point blood glucose profiles showed no significant differences between pen and syringe periods *(Figure 2)*.

Two patients experienced technical problems with their NovoPens for NPH-insulin. One patient changed her NovoPen because she thought it did not work properly — she thought that the delivery-button felt a little stiff. We examined this NovoPen but were unable to discover any technical dysfunction. Another patient changed his pen because it did not deliver any insulin after changing the Penfill. We did not have the opportunity to examine that pen.

More soluble insulin was required when the Penfill was used for NPH-insulin. The total dose was 31.3 U/day during the pen period compared to 29.9 U/day during the syringe period ($p = 0.02$). The bolus dose before breakfast was 11.1 U/day during the pen period and 10.6 U/day during the syringe period ($p = 0.04$). There were no differences in bolus doses before breakfast, lunch, dinner or evening snacks *(Table 2)*.

The patient questionnaire demonstrated that out of the forty patients 39 found it easy to resuspend NPH-insulin in the Penfill, 39 had confidence in dose accuracy, 35 found it easy to change the needle for the NovoPen and 30 found the NovoPen quicker to use than conventional syringes. When the study was finished 38 of the patients chose to continue using the NovoPen for basal insulin.

*Table 2*
*Comparison between pen and syringe periods*

| | NovoPen | Syringes | p-value |
|---|---|---|---|
| Dose soluble insulin (U) | | | |
| — before breakfast | 11.1 | 10.6 | 0.04 |
| — before lunch | 8.8 | 8.4 | N.S. |
| — before dinner | 10.5 | 10.3 | N.S. |
| — before evening snacks | 0.9 | 0.7 | N.S. |
| Total dose soluble insulin (U) | 31.3 | 29.9 | 0.02 |
| Dose NPH-insulin bedtime (U) | 18.5 | 17.7 | N.S. |
| Total insulin dose (U) | 49.8 | 48.1 | N.S. |
| Weight (kg) | 71.5 | 71.7 | N.S. |
| $HbA_{1c}$ (%) | 7.6 | 7.5 | N.S. |

*Figure 1*
*The figure shows the number of patients with different grades of hypoglycaemic events. Both treatment groups summarized*

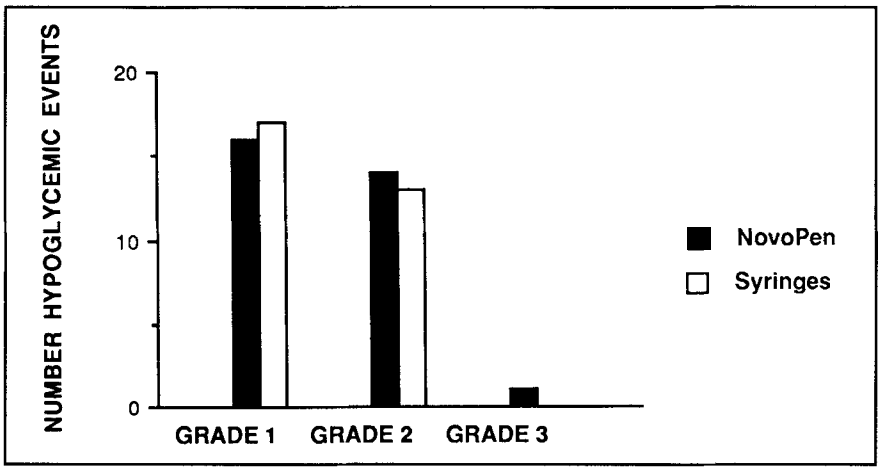
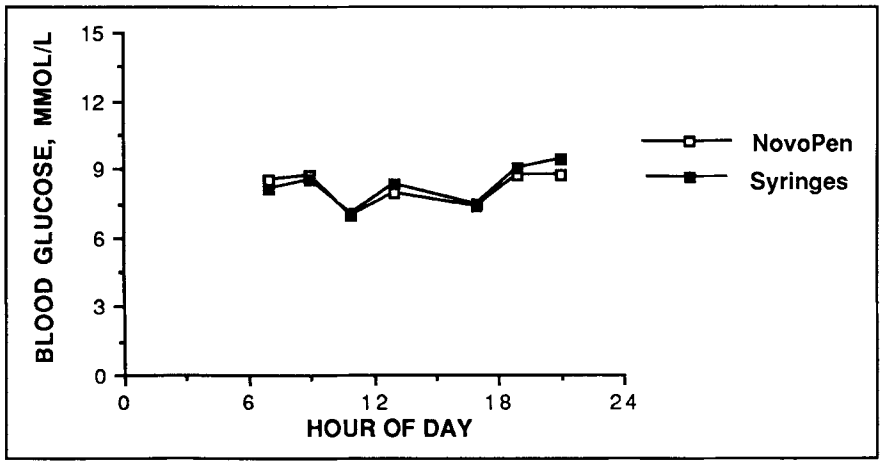



*Figure 2*
*The figure shows blood glucose levels during pen and syringe administration of NPH-insulin. Results of patients' self-recorded blood glucose measure. Both treatment groups summarized*




## Discussion

Several studies have shown that the patients find the NovoPen easier both to use and to carry than conventional syringes. They also appreciate the fact that the insulin is ready for injection which makes it more convenient to inject it discretely or unnoticed. This advantage is most important for the pre-meal injections of soluble insulin as most patients on multiple injection therapy inject their basal insulin at bedtime. The insulin pen is now also used by patients on conventional therapy and by patient groups other than those treated with multiple injection therapy.

In this study the total dose and the breakfast bolus dose of soluble insulin was slightly higher when the insulin pen was also used for NPH-insulin. However the statistical significance of this difference is hardly clinically relevant. There was no difference between morning blood glucose values during the two treatment periods even if there was a weak tendency to higher values during the pen period. The reason for this tendency could be a less successful resuspension. Our opinion is that it is very important to give the patients adequate instructions on this point. This is becoming more important with the current increasing use of insulin pens even for older patients on conventional therapy. Provided that adequate instructions how to resuspend the insulin are given, we conclude that the NovoPen is a safe, convenient and acceptable device for administration of NPH-insulin.

In this study 38 out of 40 patients chose to continue using the NovoPen for their injections of basal insulin when the study was finished. Our belief is that patients on multiple injection therapy should be offered insulin pens not only for their bolus injections of soluble insulin but also for the injections of basal insulin. Insulin pens also simplify conventional insulin treatment for those patients where the available insulin mixtures are suitable.

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