**Title: Novel Insulin Replacement Therapy with a Transdermally Delivered Human Insulin Product**

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The authors have no conflicts of interest to disclose.

**Novel Insulin Replacement Therapy with a Transdermally Delivered Human Insulin Product**

**KEY SEARCH TERMS: Insulin, transdermal insulin, needle-free delivery, reducing insulin injections, first-in-class**

## Abstract

**Context:** To test a more patient-compliant and convenient needle-free method for delivering insulin transdermally.

**Objective:** To determine whether Insulin can be supplemented transdermally (TD) on a one-to-one basis with injectable dose forms.

**Design:** Open label, multiple dose pilot Phase 0 study comparison of various formulation alternatives as measured by serum glucose levels.

**Setting:** Analytical and formulation laboratory, within a facility with on-site primary care.

**Patient:** A brittle diabetic requiring more than 300 IUs of Insulin

**Interventions:** Doses of from 10 to 1,000 IUs dosed transdermally via a novel sprayed-on, liquid medium.

**Main Outcome Measure:** Favorable comparison of insulin response when dosed transdermally versus sub-cutaneously.

**Results:** All formulations resulted in glucose modulation including delivery of commercially prepared Novolog. Test day conditions included deleting injected long-acting Insulin and deleting injected short-acting Insulin. In addition, marked flattening of serum glucose after initiation of transdermal dosing was observed.

**Conclusion:** This current project with insulin, while limited to only one subject, is believed significant on several accounts. It is clear that administration of the HypoSpray® insulin product to the skin results in a flux of human insulin in sufficient quantity to down-modulate serum glucose.

## Introduction

Millions of individuals with Types 1, 2 & 3 Diabetes around the world utilize injected insulin to manage their daily variations in serum glucose in an attempt to achieve Normoglycemia and avoid Hypoglycemia.

Heretofore, monomer human insulin at nearly 6,000 Daltons molecular weight was assumed to be beyond the capabilities of any transdermal system. This paper describes outcomes of testing 16 formulations developed and tested on a single patient described as a brittle T2D

patient on more than 20 separate occasions. The experiments demonstrate that Insulin can be supplemented transdermally on a one-to-one equivalent basis with the injectable dose form.

## Transdermal Delivery Challenges

The history of transdermal drug delivery is focused on the work of Zaffaroni[2], Maibach[3] and others who in the late 1970's demonstrated the possibility of delivering a limited number of small molecules, effective in small doses and leached in by first-order kinetics from barrier-and-reservoir or monolithic drug-in-adhesive systems across intact skin. Attempts to enhance cross-skin flux were mostly met with increased skin-sensitizing reactions or other untoward skin changes. Scientists at the Langford Research Institute, the William Harvey Institute at Barts, and the London NHS have demonstrated the ability of this system to effectively deliver large drug doses, including small peptide drugs, across intact skin via dissolving the API's in a solution formulated for the bolus of API to model certain parameters of physical chemistry, common to substances able to transmigrate intact skin. [4,5,6,7]

## Materials and Methods

The assumption in the experimental design phase was that the system would be relatively inefficient at delivering human insulin across intact skin. We had extensive experience with our original HypoSpray® Delivery System (HDS) formulation, HDS-B, but initial evaluations showed limited suitability for large molecules including insulin. While all of the shown experiments utilized the original configuration, later experimental data showed an advantage for the HDS-A system that was modified to enhance its ability to carry large doses of the insulin peptide.

Initially, preparations at very high potency were prepared. At lower doses the system succeeded in accomplishing modulation of glucose levels at virtually one-to-one ratios with products delivered via SC injection. During treatment days, serial blood samples were tested using a standard hand-held blood glucose meter with digital readout (Contour Next). Performance of the transdermal system was equivalent to Novolog administered SC (see experiment B). This validated the premise that the emerging system could reliably deliver insulin. The excerpted experiments detailed below were dosed as follows: Experiment A: Insulin USP, 797 Insulin IU/mL; Experiment B: Novolog®19.5 Insulin IU/mL; Experiment C: Insulin USP 219 Insulin IU/mL; Experiment D: Insulin USP 55 Insulin IU/mL

## Experimental

The study of physiological response to insulin therapy in Diabetes patients is complicated by the multi-variate factors affecting glucose metabolism including diet, exercise, dose schedules and other factors.

The authors determined that we must endeavor to monitor serum glucose hourly throughout the course of the study day. A commercially available blood glucose meter was used

(Contour Next, SN8296193). These meters have a validated error ratio of +/- 15 mg/dL. We also endeavored to maintain a consistent meal schedule and a standard meal each day. At all times, commercially prepared insulin was at hand to supplement dosing, if required. On experimental days, in most cases, 4-hour active insulin (Novolog®) was used to set a basal level.

**Research Ethics –** This research was conducted as Phase 0 research on an active natural substance which is not regulated per se. The research was conducted under a fully informed consent status and under the medical supervision of Dr. William Kirsh, D.O. with the necessary patient safety measures in place. The Study was reviewed and approved by the Langford Institute Institutional Review Board (IORG0006005). One of the authors is chronic Type 2 diabetic and served as the subject for all experiments. The potential risks were reviewed in detail and he determined that, given his long experience in treating himself with Insulin supplementation coupled with the fact that his insulin response is quite low, the potential benefits achievable outweighed any risk which was agreed to be minimal.

The charts following depict the potency of insulin, date, time and dosing of the various doses.

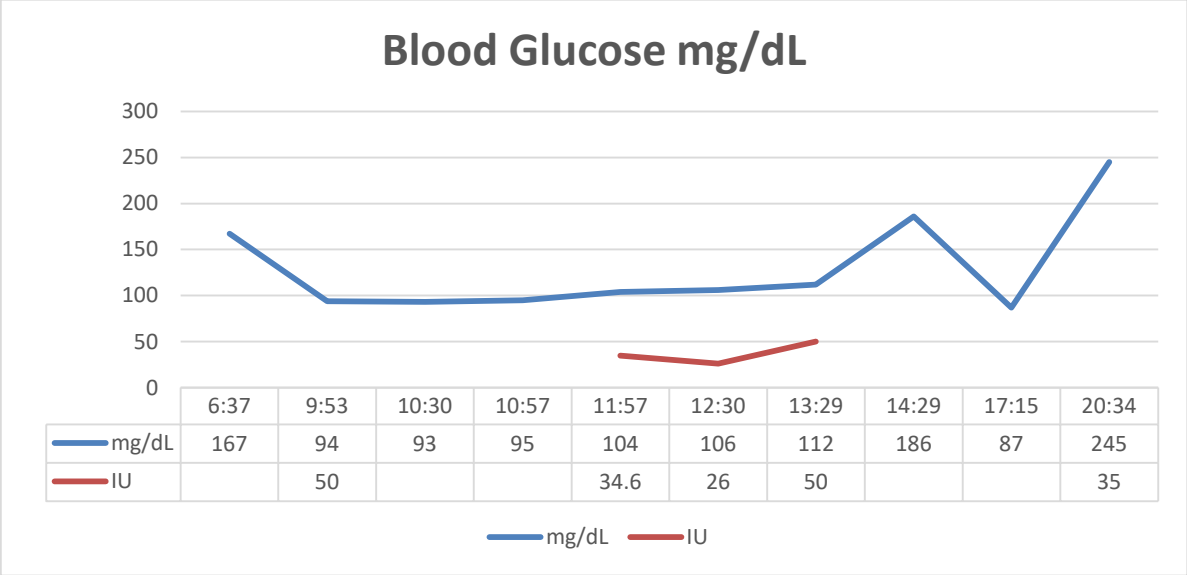
## Results

The following summarizes key metrics and findings for the studies excerpted.

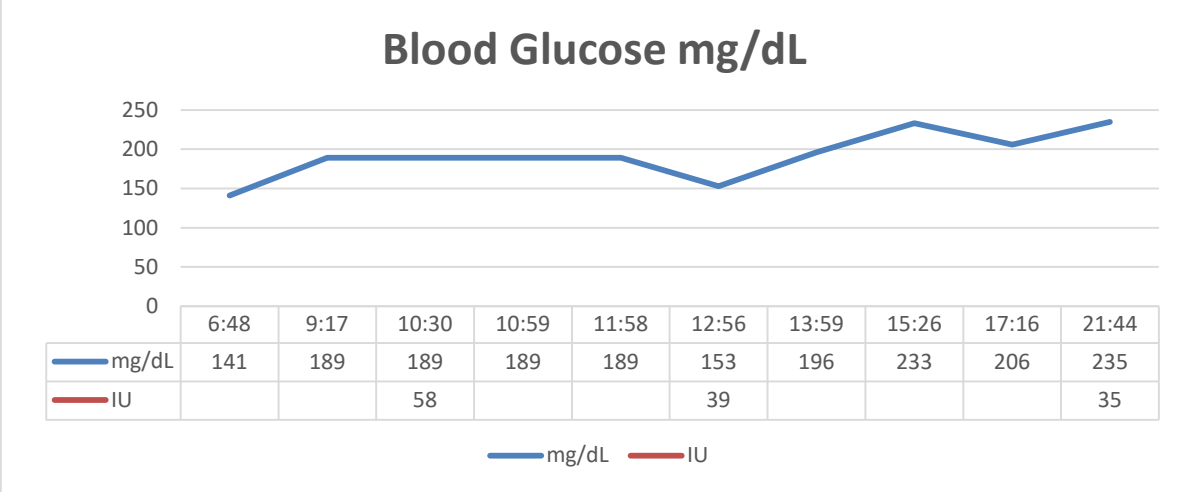
- Exp A: 797 IU/mL, Dose**:** 557 IU, No rapid drop and no rise for 2.5 hours
- Exp B**:** 20 IU / mL, Dose: 58 IU, No Novolog SC, Novolog TD, Glucose stable for 3 hours then declines 40 points.
- Exp C: 200 IU/mL, Dose: 175 IU, Dosed hourly yields flat levels, no precipitous drop
- Exp D: 60 IU/mL, Dose: 41 IU Day 1, 82 IU Day 2, Serum Glucose is modulated throughout the days with no Lantus® basal support from

**Experiment A**

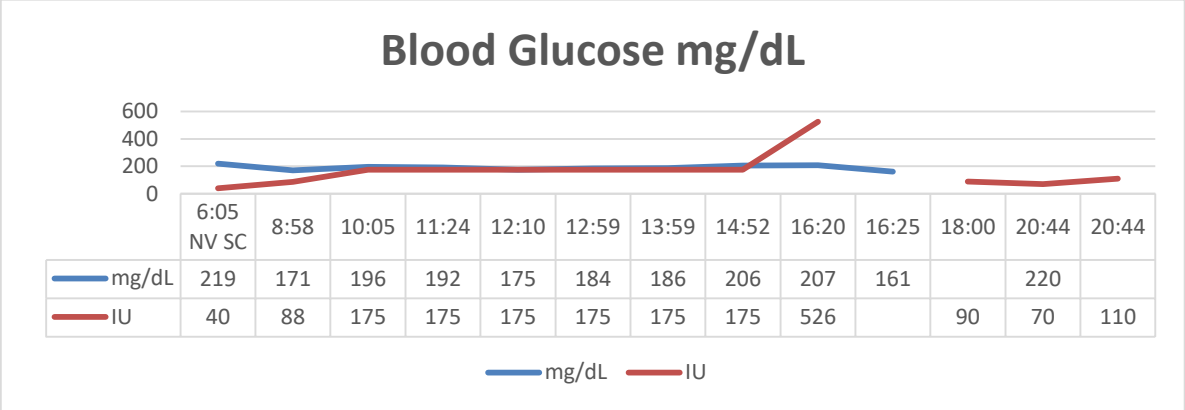



**Experiment B**

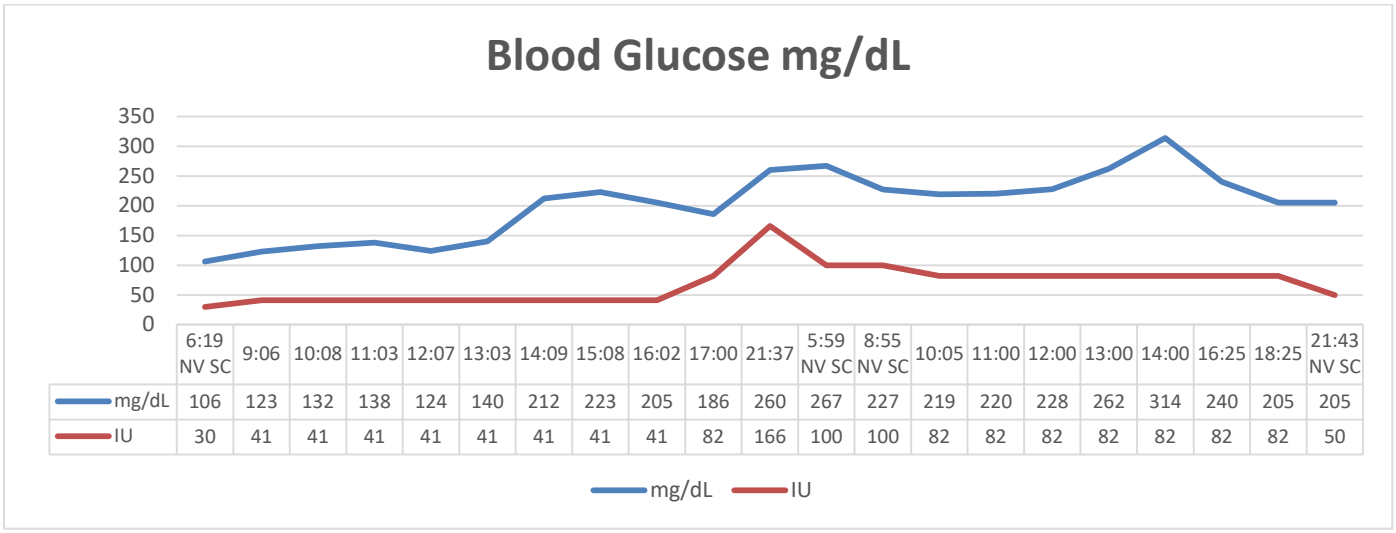


**Experiment C**




**Experiment D**




## Conclusions

Conclusions A: Blood Glucose, starting at a low baseline, after administration of transdermal insulin, demonstrated no rapid drop and no rise for 2.5 hours. On administration of 557 IU with lunch, glucose leveling was observed for one hour, and then rose 70 points at 2 hours. Administration of 50 units Novolog SC yielded a 100-point reduction at 2.5 hours on, a consistent Insulin response for this patient. Again, despite 10X dosing, no precipitous drop in blood glucose was noted. As we did not observe an insulin response proportional to our dosing, our underlying assumption at this point was the Insulin flux was low.

Conclusions B: Novolog SC was not administered on this day, yielding glucose rising at 20 mg/dL/Hr. (Lantus Basal response only). Administered 58 units of Novolog formulated into the transdermal system at 10:00 am Glucose values are stable for 3 hours then decline 40

points. Administered 39 additional units after lunch (12:56) and observed a modest 40 point rise post-prandial. An additional 33-point rise (20 points per hour) was observed followed by a decline to about baseline at 4 hours. After an observed upward slope, typical for this patient, we observed a downward trend consistent with response to insulin. No precipitous drop in blood glucose was noted. The divergence at the start (21:44 pm through 6:48 am), the observed decline in blood glucose is higher than expected for this dose. Similarly, divergence after 15:26 shows higher than expected insulin performance.

Conclusions C: Formulation adjusted to match USP potency. Initial glucose was rising at 40 mg/dL/Hr. after administering 88 IU TD. Administered 175 units transdermally hourly, to drive glucose values down. Repeated TD delivery yielded a leveling glucose value, with a pre-dinner decline, followed by a post prandial rise over five hours. Hourly doses total approximated bolus dose for the time period, showing leveling blood glucose similar to bolus dose. Insulin response initially equivalent to Novolog response.

Conclusions D: Formulation adjusted to increase a key ratio, evaluating premise that this ratio affects transdermal flux. Glucose levels modulated after administering 40-80 IU TD hourly observing some postprandial rise. No long-acting Lantus was administered for 36 hours prior to TD dosing. Insulin delivery efficiency appeared similar to a normal day with Lantus slowing glucose increase to 20 mg/dL/Hr. Blood glucose was lowered prior to start by means of increased Novolog dose.

## Discussion

Initial evaluation of the response data after doses of 500 to 1,000 IUs led the authors to conclude that very little insulin was delivered through the skin. The TD delivery of commercial Novolog without SC Novolog dosing showed insulin response comparable to SC Novolog. Experiments at 50-200 IU/ml showed TD insulin response comparable to SC injection. Finally, the system was able to modulate blood glucose without other basal exogenous insulin supplementation for multiple 24 hour periods.

## Summary Conclusion

This current project with insulin, while limited to only one subject, is believed significant on several accounts. It is clear that administration of the HypoSpray® insulin product to the skin results in a flux of human insulin in sufficient quantity to down-modulate serum glucose. Further the system achieves insulin sensitivity equal to and exceeding injectable products. In addition, the system has demonstrated a leveling of serum glucose within the margin of error of the blood testing technology, that is, +/- 15 points.

While not a definitive study, the ability to modulate glucose, including the delivery of commercially prepared products with this system, is believed significant and worthy of further investigation.

Historically the HypoSpray® system has proven reliable for over 1,000 patients for different applications, and in the delivery of Insulin, a peptide drug, there is currently no reason to expect it will perform any less well with Insulin in a broader patient population.

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**CME Exam**

1. **A fundamental goal of insulin replacement therapy is to:**
   A. Avoid peaks and troughs of blood glucose
   B. Restore normal physiological insulin secretion patterns
   C. Avoid Hypoglycemia
   D. All of the above

2. **Human insulin is assumed:**
   A. To be effective at various peptide lengths
   B. To be equally effective delivered via auto injector or insulin syringe
   C. To be too large to deliver transdermally
   D. All of the above

3. **According to experiments reported in this article:**
   A. Human Insulin and fast-acting Novolog® have been effective delivered in a patch
   B. Human Insulin and fast-acting Novolog® have been effective delivered across intact skin in a solution sprayed onto the skin
   C. Human Insulin and fast-acting Novolog® have been effective delivered by SC injection
   D. Human Insulin has been effective delivered across intact skin in a solution sprayed onto the skin

4. **It is clear that administration of the HypoSpray® insulin product to the skin results in:**
   A. No flux of human insulin in sufficient quantity to down-modulate serum glucose
   B. No achievement of insulin sensitivity equal to injectable products
   C. A. & B.
   D. None of the above

**Answers:**

1. D., All of the above
2. D., All of the above
3. B., Human Insulin and fast-acting Novolog® have been effective delivered across intact skin
4. D., None of the above

 

 