Abstract: A Comparison of Injected Insulin Replacement Therapy with a Novel Transdermally Delivered Human Insulin Product

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Overview

Millions of individuals with Types 1, 2 & 3 Diabetes around the world utilize insulin to manage their daily variations in serum glucose. The benefits of managing glucose in these patients are established medical verities. A fundamental goal of this therapy is to restore, as much as possible, "normal" physiological insulin secretion patterns, avoiding peaks and troughs of blood glucose, particularly very low levels characterized as Hypoglycemia which can be life-threatening.

Heretofore, monomer human insulin at nearly 6,000 Daltons molecular weight was assumed to be beyond the capabilities of any transdermal system. This writing describes formulations developed in series and tested on a single patient described as a brittle T2D patient with low insulin sensitivity. The experiments demonstrate that Insulin:

- Can be supplemented transdermally on a one-to-one basis with injectable;
- In fast and long-acting forms as well as Humulin can be delivered with no difference in results, obviating the need for needle injectors;
- Transdermal delivery results in flatter insulin profiles
- Transdermal dosing seems to enhance insulin sensitivity even for injected forms.

Formulation Development

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 HDS formulation (HDS-B) but initial evaluations showed limited suitability for large molecules including insulin. The HDS formulation is adjusted to tailor the dipole of the system

to optimize solubility. HDS-A was specifically developed to optimize the highest dipole and was therefore chosen for the insulin formulation development.

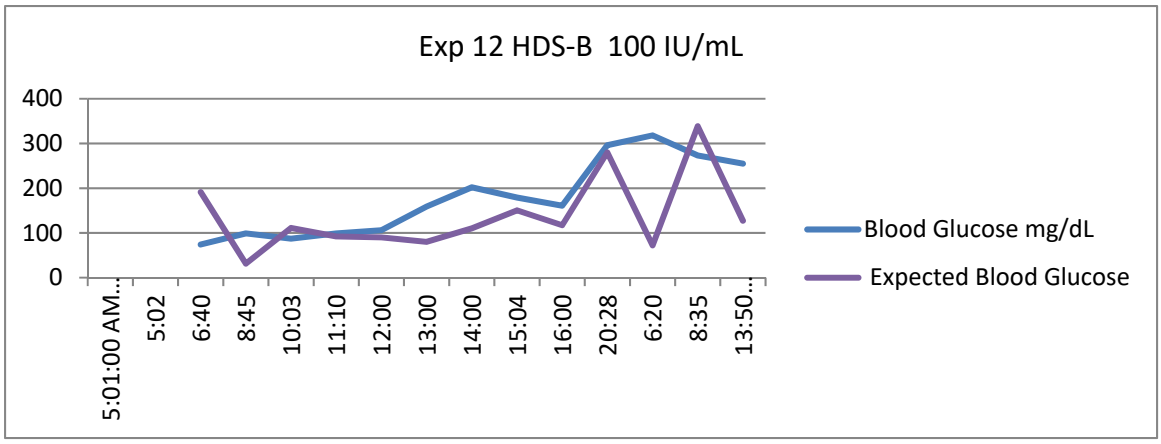
Further review of the literature led the authors to explore certain formulation variables. We proceeded to calculate additions and deletions of certain excipients and observed that an optimal ratio could be reached that enabled relatively rapid solution of Human Insulin ("Humulin") into the solvent system without agitation and further noted enhanced efficiency of the system to deliver insulin resulting in glucose down-modulation from several differing reduced concentrations of Humulin from 219 down to 54 IU/mL (Exp. 5-8).

Beginning with Experimental Formulation 11 through 17, we endeavored to optimize solvent composition and certain ratios as critical formulation parameters, for both HDS-A and HDS-B at 200 IUs per mL. This relationship was optimized using a developed calculation to inform the steps through increasing dose formulations with the differing solvent mixes. At Experiment 17 we applied the optimal composition to HDS-A for comparative purposes.

Results

A general examination of the observed vs expected glucose charts shows that the expected values generally predict lower values since nutrition and activity were not factored into the prediction. The expected values generally rejoin the observed values once nutrition has been metabolized. Observed glucose values once transdermal (TD) administration begins show leveling, i.e. constant blood glucose. This is significant:

- TD Dosing does not reduce blood glucose precipitously, even at high dosages.
- Blood glucose leveling begins from the point of TD administration,
- Leveling presents even in fasting conditions
- Insulin sensitivity decreases during TD administration, and
- Insulin sensitivity increases in the following overnight period.



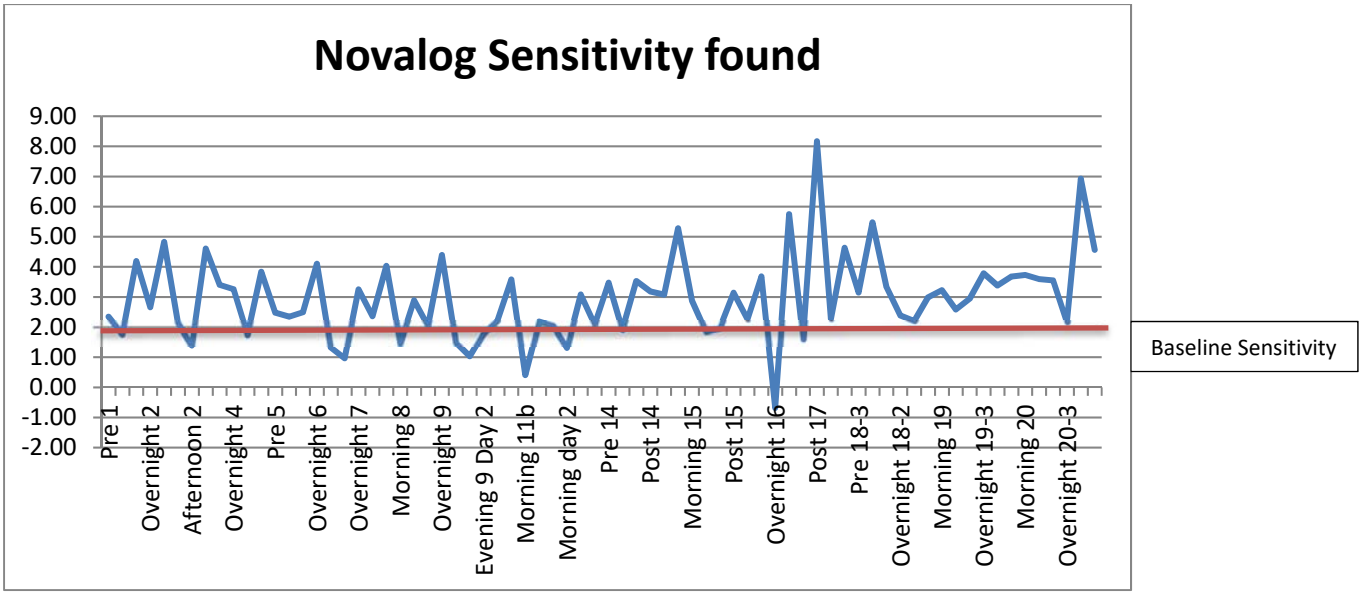
Categorical Insulin Sensitivity Results: As the TD delivery formulation was optimized, leveling was observed even at lower formulation strengths and these values were aligned with expected TD 8-hour availability insulin dosing. This leveling again clearly suggests that excess TD insulin is deposited and available for subsequent use. Novolog SC sensitivity was generally higher than TD delivered insulin (average 2.1 vs. 1.8 respectively) in the morning. These overnight values averaged 3.1 in contrast to the pre-trial point of 2.3.

Insulin sensitivity is a measure of how well the body utilized the supplied insulin. Generally this value decreases with time (subject age), and is generally treated as a long term average. To understand the TD system, Novolog sensitivity was measured before, between and during the experiments, and compared relative to the assumed sensitivity of 2. Table 4 and Figure 2 show Novolog sensitivity overnight and before TD insulin delivery, and, where available, overnight during breaks in TD dosing. Table 4 low points (sensitivity ≤ 2.1) are as follows: 16 data points ≤ 2.1 out of 48, with an average sensitivity of 3.33:

- Mornings, after breakfast
- Afternoons, after lunch
- Evenings, after dinner
- Overnight, after a 4 day hiatus in TD dosing
- Overnight, during experiment without overnight Lantus dosing

Novolog sensitivity was therefore generally much higher than pre-TD experiments and substantially higher overnight. As no treatment has shown the ability to increase insulin sensitivity, we attribute this effect to contribution from the deposited TD insulin, rather than a true shift in subject insulin sensitivity.

Figure 2 Overnight Insulin Sensitivity



Discussion

When a juvenile is diagnosed with diabetes, insulin therapy is started using the default sensitivity as established in the IU definition: One unit of insulin is defined as the amount of insulin that will lower the blood glucose of a healthy 2 kg (4.4 lb) rabbit that has fasted for 24 hours to 2.5 mmol/l (45 mg/dl) within 5 hours. Thus, multiplying IU times body mass gives the "safe" dose. Once administered the actual blood glucose response is noted and the actual patient sensitivity is calculated. This dose is "safe" since no diabetic will exhibit higher insulin sensitivity than a healthy person.

Thus as noted above, we attribute the higher "insulin sensitivity" observed due to TD insulin being stored perhaps in the Interstitium, for eventual use. In each and every case where TD insulin is initiated, leveling was observed. The SC insulin's achieved blood glucose value becomes the benchmark leveling maintained by the TD insulin's effect. By targeting the Insulin value with the SC administration, subsequent TD delivery was able to maintain leveling of blood glucose values. TD insulin complements traditional SC dosing and this synergy has beneficial effects in blood glucose management.

In the future it would be of interest to evaluate Long-acting Insulin performance via TD administration, having already established the ability to formulate Lantus into the TD system.

The analyzed results of the 20 trials unequivocally establish the ability of the HypoSpray® system to deliver insulin across intact skin and create a physiological reaction once in tissue in this subject. The patient responded when both long-acting and fast acting insulin was deleted. In addition examination of the frequency histograms reveals an unusual phenomenon, namely, there is a distinct leveling of serum glucose that is encountered when the TD Insulin product reaches effect. This leveling established by the HypoSpray dosing, creates a floor below which Serum Glucose will not fall, thereby avoiding hypoglycemia. This leveling is inconsistent with the patient's ordinary response to insulin supplementation which can be fairly characterized as a more-or-less gentle up-slope during the day.

Another interesting novelty emerges from the clinical work. Initial evaluation of the response data after doses of 500 to 1,000 IUs led the authors to conclude that very little Insulin must actually be getting through the skin. Later evaluation, once a statistical basis for the differential equation was developed, revealed that, in fact, the Insulin was being delivered, at least at higher concentrations than expected, and detectable as an extended enhanced Insulin response indicative of some amount of tissue deposition. As Insulin is routinely stored in corporal lipid tissues for ready release to the muscle cells as required, this outcome would not be inconsistent with normal physiologic response.

The patient's insulin sensitivity was calculated from early-morning pre-prandial dosing of an injectable dose form (Novolog®) and the overnight effect of long-acting insulin (Lantus®) and are consistent with the patient's own estimation of his sensitivity at 2 mg Glucose/IU Insulin/Hour. This measure continued to be a reliable gauge and predictor of his response to both types of products and dose forms throughout the studies. It is also notable that when the patient reverted to only SC dosing of Novolog and Lantus on weekends or during other hiatus, his response to SC insulin dosing was the generally the same as before with a notable exception. Examination of the clinical data shows that on days when HypoSpray insulin dosing was hourly and/or the dose was high (160-200 IU), the response to injected insulin overnight was similar to the days' pattern of response, that is, the leveling that was established by the HypoSpray® dosing was seemingly holding in effect for some hours after HypoSpray® dosing was halted. Similarly when the dosing schedule was prn and at lower doses (20-50 IU), leveling response during transdermal dosing was less than observed with hourly dosing and larger doses, and less dissimilar to response to SC dosing of 4 hour insulin. This supports the authors' theory that some Insulin is being stored in the Interstitium.

This latter phenomenon, if borne out in other patients, along with the presentation of the leveling serum glucose, may indicate that this transdermal approach is re-enabling access to stored or bound Insulin in the Interstitium. This may be understood similar to other steroid hormones such as Testosterone, where a balance between free and binding-globulin bound hormone is not sufficiently engaged to drive the serum values back to a "normal" baseline of 60-100 mg/dL. If this theory is proven, in future, insulin-dependent diabetics may gain some flexibility from constant checking of the blood and may be able to set their insulin "thermostat" by injecting insulin to gain a safe target of 80 to 120 mgs of Glucose/mL then maintain leveling with the HypoSpray® product.

It is also significant that when delivered with the TD system transdermally, the commercially prepared Novolog obtained normal results as regards response but also showed the now characteristic leveling.