Efficacy and Safety of a Mixture of Two Different Brands of Insulin Products in Patients with Type 1 Diabetes Mellitus

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Background: In the past, insulin products manufactured by different companies were considered to be incompatible. However, no studies have actually been conducted on insulin product compatibility. The objective of this study was to determine the efficacy and safety of a mixture of insulin products produced by different companies in patients with diabetes mellitus.

Methods: Chart reviews were conducted on 105 patients with type 1 diabetes mellitus who were followed up at Taichung Veterans General Hospital between October 1999 and December 2001. Twenty patients were included for final analysis. The average daily insulin requirement, hemoglobin A₁c (HbA₁c) level, body weight, and body mass index (BMI) were compared 6 months before (period 1, used same brand of insulin, Humulin N plus Humulin R) and after (period 2, used different brands of insulin, Insulatard HM plus Humulin R) the mixture treatment. Hypoglycemia and other adverse events were also recorded.

Results: The difference in average daily insulin requirement (intermediate-acting, short-acting) between periods 1 and 2 was not statistically significant (27.1 ± 10.8 U vs 27.1 ± 10.8 U, \( p = 0.317 \); 13.9 ± 7.6 U vs 14.7 ± 7.3 U, \( p = 0.655 \)). There was no significant difference in HbA₁c level between periods 1 and 2 (8.0 ± 1.5% vs 8.0 ± 1.2%, \( p = 0.732 \)). The difference in BMI between periods 1 and 2 was not statistically significant. The number of hypoglycemic events 6 months before and after the mixture therapy was also not statistically significantly different. There were no reported injection-site reactions or an increased number of adverse events when using the mixture of Insulatard HM and Humulin R.

Conclusion: This retrospective study demonstrated that using a mixture of different brands of insulin (Insulatard HM plus Humulin R) for 6 months did not change the efficacy of insulin in patients with type 1 diabetes mellitus.


Key Words: brand, company, efficacy, insulin, safety

Introduction

Almost all insulin products worldwide are now produced by 2 companies, Eli Lilly (Indianapolis, IN, USA) and Novo Nordisk (Bagsvaerd, Denmark). These 2 manufacturers independently add different bases or solvents to their insulin products in spite of their similar antihyperglycemic duration after subcutaneous injection (i.e. short-acting or intermediate-acting insulin). Generally, it is thought that insulin products from different companies should not be mixed together because of potential incompatibility of the additives that may interfere with the hypoglycemic effect or induce adverse reactions. In reality, a hospital or pharmacy may purchase insulin from different manufacturers. Patients are usually unaware of this issue and may use a mixture of insulin from different sources. It has been reported that pharmacists may dispense...
insulin from different manufacturers, with the only consideration being their comparable drug effects.\textsuperscript{1,3} Solubility can be reduced when short- and long-acting insulin made by the same company are mixed, and the onset of action of the short-acting insulin may, thus, be delayed.\textsuperscript{4,5} However, the efficacy and safety of using a mixture of short-acting and intermediate-acting insulin products made by 2 different companies have not been reported in the literature. The aim of the present study was to evaluate the efficacy and safety of an insulin mixture of Humulin R (Eli Lilly) and Insulatard HM (Novo Nordisk) in a hospital-based diabetic population.

**Methods**

Chart reviews were conducted on 105 patients with type 1 diabetes mellitus who had received regular follow-up at Taichung Veterans General Hospital between October 1999 and December 2001. Twenty patients were included in the final analysis. The inclusion criteria were as follows: (1) had adhered to the regimen of the mixture of Humulin N plus Humulin R (Eli Lilly) for more than 6 months, and then shifted to the mixture of Insulatard HM (Novo Nordisk) plus Humulin R for more than 6 months; (2) the dosage of Humulin N plus Humulin R was fixed for more than 6 months before shifting to the mixture of Insulatard HM plus Humulin R; (3) not taking any other regular medication and had no other systemic disease; and (4) free of diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and cardiovascular disease. The exclusion criteria were: (1) impaired renal function, with serum creatinine more than 2 mg/dL; and (2) clinical evidence of active liver disease, or serum alanine aminotransferase/aspartate aminotransferase 2 or more times the upper limit of normal. All of the 20 patients were treated with a twice daily insulin regimen of a mixture of short-acting and intermediate-acting insulin.

The average daily insulin requirement, hemoglobin A\textsubscript{1c} (HbA\textsubscript{1c}) level, body weight, and body mass index (BMI) were compared 6 months before (period 1, used same brand of insulin, Humulin N plus Humulin R) and after (period 2, used different brands of insulin, Insulatard HM plus Humulin R) the mixture treatment. HbA\textsubscript{1c} was measured by high performance liquid chromatography using a Diamat analyzer (Primus CLC385; Primus Corp, Kansas City, MO, USA). The coefficient of variation was less than 3%. The frequency of hypoglycemic or other adverse events, according to the medical charts, was also recorded. Hypoglycemia was defined as a blood glucose level below 2.8 mmol/L (50 mg/dL) or prompt recovery from the symptoms of hypoglycemia after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as hypoglycemia that developed from 12:00 pm on 1 day to 6:00 am on the next day. Since many patients included in this study were children younger than 6 years old, the hypoglycemic events may have been reported by the patient’s family. We focused on the admission notes to define any hypoglycemic event. Other adverse events, including injection-site reactions which were defined as “local erythematous change or swelling”, were noted from the charts.

**Statistical analysis**

Data are presented as mean ± standard deviation (SD). The Wilcoxon signed rank test was used for comparison of paired data before and after variance. Analyses were performed with SPSS version 10.1 (SPSS Inc, Chicago, IL, USA). Statistical significance was considered as \( p \) less than 0.05.

**Results**

The 20 patients included 13 males and 7 females with a mean age of 11.8 ± 3.7 years. Their clinical characteristics and the results of this study are summarized in Table 1. The average daily intermediate-acting insulin requirement 6 months before the

| Table 1. Characteristics of 20 patients before and after using the mixture of Insulatard HM plus Humulin R* |
|---------------------------------------------------------|--------------------------|---------------------------|--------|
| **Before**                                             | **After**                | **p**                     |
| Body weight (kg)                                       | 36.4 ± 16.3              | 38.6 ± 16.0               | 0.001  |
| Height (cm)                                            | 137.3 ± 20.3             | 141.0 ± 20.6              | < 0.001|
| Body mass index (kg/m\(^2\))                         | 18.3 ± 3.9               | 18.6 ± 3.6                | 0.126  |
| Intermediate-acting insulin dosage (U)                 | 27.1 ± 10.8              | 27.1 ± 10.8               | 0.317  |
| Short-acting insulin dosage (U)                        | 13.9 ± 7.6               | 14.7 ± 7.3                | 0.655  |
| Hemoglobin A\textsubscript{1c} (%)                     | 8.0 ± 1.5                | 8.0 ± 1.2                 | 0.732  |

*Data are presented as mean ± standard deviation.
initiation of the mixture (period 1) was not different from the average daily requirement 6 months after the initiation of the mixture (period 2). The dosage was the same before and after the mixture of insulin in 19 patients (95%); 1 patient had an increased dosage of intermediate-acting insulin after the initiation of the mixture. The average daily short-acting insulin requirement in period 1 was also not altered compared with the average daily requirement in period 2. The dosage was the same before and after the mixture of insulin in 18 patients (90%). The insulin dosages for each individual are shown in Table 2.

There were no significant changes in the HbA1c level between periods 1 and 2. The HbA1c level improved in 9 patients (45%) after using the mixture of Insulatard HM plus Humulin R, and the condition of 11 patients (55%) worsened under the same insulin dosage.

There was an increase in body weight from periods 1 to 2 (36.4 ± 16.3 kg vs 38.6 ± 16.0 kg, p = 0.001). However, there was no statistically significant change in BMI between the 2 periods.

**Safety**
The mixture of Insulatard HM plus Humulin R was well tolerated. Injection-site reactions were not reported in any patient. No patient was admitted due to hypoglycemia within the study period. The only adverse event was in a patient who suffered from 1 episode of hypoglycemia with the symptoms of cold sweating and hunger during period 2. This patient recovered after taking some carbohydrates. The incidence of nocturnal hypoglycemia after using the mixture of Insulatard HM plus Humulin R did not increase.

**Discussion**
The results of this study showed that under the same dosage, glycemic control with a mixture of Insulatard HM plus Humulin R for 6 months was not worse than with a mixture of Humulin N plus Humulin R. Using the mixture of Insulatard HM and Humulin R for 6 months did not reduce the efficacy of the insulin. However, this study did not determine the efficacy and safety of more long-term use of this mixture.

Protamine insulin (i.e. Insulatard HM, Humulin N) was introduced in 1936 as a preparation of insulin that did not require multiple daily injections. The development of the insulin assay technique led, however, to the demonstration of fast and highly regulated changes in serum insulin concentrations,
particularly at meal times, and hence to the widespread adoption of twice-daily injections of mixtures of intermediate-acting insulin together with short-acting insulin. Such a regimen was proposed in 1937 and administered in the 1960s for the management of more severe diabetes.

The active substance in Insulatard HM is human insulin produced biosynthetically (i.e. by recombinant DNA technology). It also contains other substances, including protamine sulfate, zinc chloride, disodium phosphate dihydrate, metacresol, phenol, sodium hydroxide and hydrochloric acid. Its pH is between 7.3 and 7.5. Humulin R is a clear, water-like active substance produced by a recombinant DNA technique. It also contains other substances including m-cresol (distilled 2.5 mg/mL) and glycerol. Its pH is between 7.0 and 7.8. In previous studies, mixing insulin zinc suspensions in the same syringe with soluble insulin resulted in an impairment of the quick action of the soluble component. However, the absorption and activity of regular human insulin is not diminished in mixtures of protamine insulin and regular human insulin.

In this study, we demonstrated for the first time that a mixture of insulin products manufactured by different companies (Insulatard HM plus Humulin R) can be used without reduced efficacy for a limited period of at least 6 months.

George et al. reported that switching from porcine to human insulin did not increase the number of episodes of nocturnal or reported hypoglycemia in type 1 diabetes. However, switching from a mixture of human insulin products made by the same company to a mixture from different companies has not been previously reported. Our results show that such a switch does not increase the frequency of hypoglycemic episodes for a limited period of at least 6 months. However, due to the small number of patients in this study, a randomized controlled double-blind clinical trial with a larger number of patients is needed.

Patients’ mean body weight after using the mixture of different companies’ insulins was increased. However, as most of these patients were children, it is to be expected that body weight would increase progressively as the children grew. There was no statistically significant change in BMI pre- and post-mixture.

In 1 study, a short course of exogenous human insulin induced insulin antibody in 92% of type 1 diabetes mellitus patients. Severe antibody-mediated human insulin resistance has also been reported in the literature. In this study, insulin antibody was not checked because this examination is not available in this hospital. Consequently, this study could not determine the influence of the mixture on the formation of insulin antibody.

We conclude that a preparation of Insulatard HM and Humulin N, when used in a twice-daily regimen together with Humulin R for 6 months, is of equal efficacy and safety in the management of type 1 diabetes mellitus. However, further study is needed to determine the efficacy and safety of the mixture of Insulatard HM plus Humulin R for long-term usage.

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