Use of Rapid-acting Insulin Analog as the Baseline Infusion During Glucose Clamping Improves Pharmacokinetic Evaluation

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ABSTRACT

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INTRODUCTION

The hyperinsulinemic-euglycemic clamp was proposed by Andres, et al. 1 and further advanced by deFronzo, et al. 2 The objective is to administer insulin by IV infusion to a level that suppresses hepatic glucose production, allowing the assessment of insulin sensitivity. The hyperglycemic clamp can additionally be used to assess insulin secretion; in this case, the technique requires a separate infusion of euglycemic glucose to maintain capillary glucose at 10 to 11 mM. As in the previous regular human insulin was then dosed as inhaled insulin or subcutaneously. For this study, the hyperinsulinemic-euglycemic clamp was used to compare the pharmacokinetics and pharmacodynamics of insulin lispro with those of regular human insulin. The studies reported here were conducted using a manual hyperinsulinemic-euglycemic clamp. The first study was conducted in subjects with type 1 diabetes. By protocol, in a minimum of 3 days prior to the study, participants received study insulin only when used in type 1 diabetes, the first cohort of subjects, the infused insulin was regular human insulin; for the second cohort of subjects, the infused insulin was insulin lispro. When the insulin infusion rate is fixed, the amount of glucose infused will depend on the subject’s insulin sensitivity. The hyperinsulinemic-euglycemic clamp was proposed by Andres, et al. 1 and further advanced by deFronzo, et al. 2 The objective is to administer insulin by IV infusion to a level that suppresses hepatic glucose production, allowing the assessment of insulin sensitivity. The hyperglycemic clamp can additionally be used to assess insulin secretion; in this case, the technique requires a separate infusion of euglycemic glucose to maintain capillary glucose at 10 to 11 mM. As in the previous study, regular human insulin was then dosed as inhaled insulin or subcutaneously. For this study, the hyperinsulinemic-euglycemic clamp was used to compare the pharmacokinetics and pharmacodynamics of insulin lispro with those of regular human insulin. The studies reported here were conducted using a manual hyperinsulinemic-euglycemic clamp. The first study was conducted in subjects with type 1 diabetes. By protocol, in a minimum of 3 days prior to the study, participants received study insulin only when used in type 1 diabetes, the first cohort of subjects, the infused insulin was regular human insulin; for the second cohort of subjects, the infused insulin was insulin lispro.

METHODS AND MATERIALS

The studies reported here were conducted using a manual hyperinsulinemic-euglycemic clamp. The first study was conducted in subjects with type 1 diabetes. By protocol, in a minimum of 3 days prior to the study, participants received study insulin only when used in type 1 diabetes, the first cohort of subjects, the infused insulin was regular human insulin; for the second cohort of subjects, the infused insulin was insulin lispro. When the insulin infusion rate is fixed, the amount of glucose infused will depend on the subject’s insulin sensitivity. The hyperinsulinemic-euglycemic clamp was proposed by Andres, et al. 1 and further advanced by deFronzo, et al. 2 The objective is to administer insulin by IV infusion to a level that suppresses hepatic glucose production, allowing the assessment of insulin sensitivity. The hyperglycemic clamp can additionally be used to assess insulin secretion; in this case, the technique requires a separate infusion of euglycemic glucose to maintain capillary glucose at 10 to 11 mM. As in the previous study, regular human insulin was then dosed as inhaled insulin or subcutaneously. For this study, the hyperinsulinemic-euglycemic clamp was used to compare the pharmacokinetics and pharmacodynamics of insulin lispro with those of regular human insulin. The studies reported here were conducted using a manual hyperinsulinemic-euglycemic clamp. The first study was conducted in subjects with type 1 diabetes. By protocol, in a minimum of 3 days prior to the study, participants received study insulin only when used in type 1 diabetes, the first cohort of subjects, the infused insulin was regular human insulin; for the second cohort of subjects, the infused insulin was insulin lispro.

RESULTS

The hyperinsulinemic-euglycemic clamp is an extremely useful scientific tool for the study of insulin pharmaceutics and pharmacodynamics. When used to evaluate exogenously administered test insulins, one of the challenges has always been how to account for the infused "basal insulin." Using the hyperinsulinemic-euglycemic clamp as outlined in this poster, the use of insulin lispro as the infused basal insulin alleviates much of this problem by minimizing or removing the basal insulin from the measured insulin exposure. When used in type 1 diabetes, there is no basal insulin to account for insulin resistance. When used in non-diabetic and type 2 diabetes, 2 insulins, it is possible for insulin lispro to adequately suppress the endogenous insulin to a point to enable accurate measurement of exogenously administered test insulins.

REFERENCES