PROTOCOL
HUMALOG® MIX50/50™ FOR THE TREATMENT OF INSULIN REQUIRING GESTATIONAL DIABETES

RATIONALE

Controlling hyperglycemia during pregnancy decreases the risk of adverse neonatal and maternal outcomes. Not only must fasting glucose be normalized, but clinical evidence also indicates that controlling postprandial hyperglycemia will significantly reduce the risk of adverse neonatal and maternal outcomes (1-2).

Standard therapy to achieve near-normal glycemia in gestational diabetes involves combining intermediate-acting basal (NPH) insulin with rapid-acting insulin (insulin lispro), thereby requiring 6 daily injections (Figure 1). Premixed Humalog® Mix50/50™ has the potential advantage over combination rapid-acting plus NPH insulin because it involves fewer injections, and those injections are associated with mealtime (Figure 2). The potential downside to the premixed formulation is nocturnal hypoglycemia associated with the time lag between the dinner and breakfast dose. This study will evaluate the efficacy and safety of Humalog® Mix50/50™ compared to that of Humalog® plus Humulin N® insulin for the treatment of insulin-requiring patients with gestational diabetes mellitus, while monitoring glucose control, intrauterine growth and assessing pregnancy outcomes.

PREVIOUS WORK

The principal investigator has established nationally-recognized protocols for the care of pregnant women with diabetes (3-6) and has played an active role in the field of gestational diabetes (7-9). Thus she is uniquely positioned to study the potential efficacy of new therapies for gestational diabetes. Two studies have particular relevance to the proposed research and are attached to this application. Jovanovic and colleagues studied the metabolic and immunologic effects of insulin lispro in gestational diabetes (10) by randomizing women to receive either regular human insulin or insulin lispro before consuming a test meal. The study proved the safety of insulin lispro for women with gestational diabetes. In a subsequent study led by Pettitt (11), postprandial glycemic control was demonstrated in women with gestational diabetes taking insulin aspart via higher insulin peak and lower demand on endogenous insulin secretion.

STUDY HYPOTHESIS

Humalog® Mix50/50™ administered as 3 injections daily is equivalent to Humalog® plus Humulin N® insulin administered as 6 separate injections daily in terms of glucose control, but may have some advantages due to increased ease of use.

PRIMARY OBJECTIVE

Compare the efficacy and safety of three daily injections of Humalog® Mix50/50™ to six daily injections of Humalog® and Humulin N® insulin, by fasting glucose measurements.

SECONDARY OBJECTIVES

1. Compare incidence of maternal hypoglycemic events between the two treatment arms.
2. Compare neonatal outcomes between the two treatment arms.
3. Compare fetal fat measurements between the two treatment arms.
4. Compare adherence rates and patient acceptability of the two injection regimens
5. Compare A1C between groups at end of protocol and within groups at baseline versus end of protocol.

STUDY DESIGN

Women diagnosed with gestational diabetes receive diet and exercise education. They are instructed to record their pre- and post-prandial glucose measurements obtained by fingerstick. Following one week of diet and exercise therapy, patients with fasting glucose levels >90 mg/dL or postprandial glucose level >120 mg/dL will be recruited to this study.

Inclusion Criteria

- Pregnant and at least 13 weeks gestation
- Diagnosed with gestational diabetes[1]
- Failed diet therapy

Exclusion Criteria

- pregnant women <18 years old or over 45 years old
- a urine dipstick urine with >2+ protein
- blood pressure >140/80 mmHg; hematocrit <30%
- refusal to take insulin
- inability to understand instructions or to consent to participate.

METHODS

Subjects will be randomized 1:1 to receive usual insulin treatment of six injections daily (Humalog® injected three times daily before meals plus Humulin N® insulin injected at 8am, 4pm and midnight) as diagrammed in Figure 1, or 3 injections of Humalog® Mix50/50™ (injected only before meals) as diagrammed in Figure 2.

Baseline measures will include glucose tolerance test data, height, weight, and A1C by DCA2000+. In addition to the standard instruction to test blood glucose pre- and one-hour postprandial, all participants will be asked to test blood glucose levels at 3 a.m. Patients on the Humalog® Mix50/50™ arm of the study will be initially prescribed insulin doses of 0.3 times their weight in kilograms to be taken before each of three meals. Those on the standard therapy arm will be initially prescribed insulin doses calculated at 0.15 times their weight in kilograms for each of their 6 injections.

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[1] We shall use American Diabetes Association criteria for diagnosis of GDM: blood glucose concentration >140 mg/dL one hour after administration of a 50 gram glucose load, followed by an oral glucose tolerance test (OGTT) in which 2 or more of the readings are at or above 95 mg/dL fasting, 180 mg/dL at one hour, 155 mg/dL at 2 hours and 145 mg/dL 3 hours after administration of a 100 gram glucose load (12).

Participants will be seen weekly for adjustment in dosages based on their food records, downloaded glucose monitor data and Al C levels. Subjects in the study group whose fasting glucose exceeds 90 mg/dl will be prescribed Humalog® Mix75/25™ at their evening meal rather than Humalog® Mix50/50™. Subjects will be discontinued from the study if their 3 a.m. blood glucose concentration falls below 55 mg/dL that is unresponsive to a snack at bedtime or if their fasting blood glucose is greater than 90mg/dL despite increasing doses of Humalog® Mix50/50™ at the evening meal followed by treating with Humalog® Mix75/25™ at the evening meal.

Maternal weight will be recorded at each visit. Participants will be asked to bring their supply of insulin pens to every other visit, for which they will be paid ten dollars to maximize cooperation with this essential aspect of the research. The insulin pens will be counted as measures of adherence.

Consent forms of enrolled patients will be given to the hospital at prenatal enrollment and will be part of their hospital medical chart at the time of delivery. Delivery room nurses will be instructed to collect cord blood and notify the study coordinator of the birth. Data collected from the birth will include sex of the baby, gestational week, ethnicity, length, birthweight and mode of delivery. Neonates will be assessed for macrosomia and hypoglycemia. Maternal postpartum glucose levels will be recorded.

SAMPLE SIZE

40 women will be recruited into the study in order to achieve at least 30 evaluable subjects (15 in each treatment arm) over the 12 months duration of the study. Based on the standard deviation for fasting glucose concentrations reported from the NHANES II study, measurable data from 30 subjects (15 in each group)will have 80% power to find an inter-group difference as small as 8 mg/dL at a p-value of 0.05 (13).

PRIMARY EFFICACY MEASURES

The primary measure used to substantiate the primary study objective will be maternal glucose control as reflected by fasting values from glucose monitor data.

SECONDARY EFFICACY MEASURES

The maternal A1C will be measured by Bayer DCA2000+ at baseline and at end of protocol. The 3 a.m. glucose records will be assessed for nocturnal hypoglycemia. Maternal weight gain will be assessed as an indicator of over-insulinization. In addition, we will analyze baby birth weight percentile, APGAR scores, cord blood insulin levels and mode of delivery as measures of fetal outcome. We will use insulin pen count data as an indicator of maternal adherence to the therapy regimen.

STATISTICAL ANALYSIS

Data analysis will be done using SAS for Windows version 9. Differences between groups in continuous variables (glucose, A1C, birth weight etc.) will be compared with t-tests and potential confounders (age, race/ethnicity etc.) will be controlled for with linear regression. Differences in categorical variables (hypoglycemic events, macrosomia, type of delivery

etc.) will be evaluated using chi-square or Fisher's tests as appropriate. Our tests will be testing the hypothesis that the two treatments are different and the null hypothesis will be equivalence.

ANTICIPATED FINDINGS

We anticipate maternal and fetal outcomes with the Humalog® Mix50/50™ will be equivalent or non-inferior to standard insulin therapy due to the convenience of three injections rather than six per day. The risk of possible increased hypoglycemia, particularly during the night, however, needs to be carefully assessed.

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