Feeding preterm infants is a formidable task because of their gastrointestinal (GI) immaturity. Previous studies have shown that a number of their GI functions are underdeveloped compared with those of the term infant. GI functions such as lactase activity and motor function undergo their most significant development during the last trimester. Animal studies have shown that maternal milk contains a number of factors that can enhance development of the immature GI tract. Of these, insulin is present in maternal milk at levels three to fourfold higher than in maternal blood. Insulin has been shown both in vitro and in vivo to accelerate a number of GI functions. More recently, enteral administration of insulin to newborn pigs and rats has been shown to enhance development of intestinal activity and growth.

The present pilot study was carried out to determine whether enteral administration of insulin to preterm infants would enhance gastrointestinal development and reduce feed intolerance. A large, randomised, placebo controlled trial would enhance their gastrointestinal development and reduce feed intolerance. Whether enteral administration of insulin to preterm infants would enhance development of intestinal activity and growth.

MATERIALS AND METHODS

Study population

Two groups of infants were compared. Eight insulin treated infants were enrolled during 1997. They were selected sequentially from the Texas Children's Hospital nursery by criteria used in a prospective feeding trial in 1992–1997. The infants recruited met the following criteria: 26–30 weeks gestation, determined by a combination of maternal dates and early antenatal ultrasound; gestational age agreement between the two methods of two weeks or less; appropriate size for gestational age; postnatal age ≤ 96 hours; absence of major congenital malformations; and fraction of inspired oxygen < 0.60 at 72 hours.

Matched control infant data were obtained from the prospective feeding trial performed in 1992–1997. Infants from the feeding trial were used as controls in order to obtain comprehensive data on a large number of infants. Of the 171 infants enrolled in this feeding trial, 80 were found to match the insulin treated infants in terms of gestational age, birth weight, age at which feeds were started, proportion of feeds that were human milk, and feeding method (intermittent bolus every three hours). The study was approved by the Baylor College of Medicine institutional review board for human subject research.

Study design

Insulin treated infants received 1 U/kg regular human insulin (Humulin; Eli Lilly & Co, Indianapolis, Indiana, USA) every six hours. The insulin was given through the nasogastric feeding tube, followed by the infant’s usual feed. Insulin administration was begun at 4 days of age and continued to 28 days of age. The dose and duration were based on preliminary studies carried out in newborn pigs.

Feeding protocol

Feeds were begun in both groups of infants when they were clinically stable (about 10 days of age). The initial feeding volume was 20 ml/kg/day and the volume was increased by that amount daily until complete enteral feeding was achieved. Parenteral nutrition was used until the infants achieved complete enteral feeds, and was adjusted to provide a total intake (enteral and parenteral) of 120 kcal/kg/day. The infants received either human milk or Enfamil Premature Formula (Mead-Johnson Nutritional Division, Evansville, Indiana, USA) if the mothers had inadequate milk production. Management of the infants was at the discretion of the attending neonatologists without input from the investigator.
Standard care of infants in the nursery did not change appreciably over the observation period. In addition, the large number of neonatologists at the institution helps to ensure that no one doctor has an inordinate influence on patient care.

**Effect of insulin on blood glucose**

To determine the effects of enteral insulin on serum glucose concentration, they were measured at 0, 30, and 90 minutes after the first, second, and fifth doses of insulin.

**Measurement of lactase activity**

Intestinal lactase activity in both groups of infants was determined at 28 days of age using the method of Weaver et al. This method has been validated by comparison with direct measurements of lactase activity in biopsy specimens of small intestine in the same patients. In addition, changes in the ratio correlate with clinical observations on disaccharidase activity. I have made similar observations in newborn pigs (unpublished data). To account for any variation in the intake of lactose and lactulose, the lactulose/lactose ratio was expressed as that measured in the urine versus that measured in the milk. Thus the higher the lactase activity, the higher the urine to milk ratio of lactulose/lactose.

The lactulose/lactose solution was administered for a total of 30 hours. During the last six hours, all urine was collected continuously as previously described, and stored at −20°C with 0.1 ml sodium merthiolate until analysed.

**Measures of feeding intolerance**

Measures of feed intolerance were monitored throughout the hospital stay for both groups. For the insulin treated infants and the controls, decisions to withhold feeds because of feed intolerance were made by the attending doctor according to a published algorithm. Given that term infants rarely experience feeding difficulties, it is accepted that feed intolerance is related to feed intolerance. Given that term infants rarely experience feeding difficulties, it is accepted that feed intolerance is related to GI immaturity. A large part of the morbidity associated with preterm birth is related to feed intolerance. Given that term infants rarely experience feeding difficulties, it is accepted that feed intolerance in the preterm infant is related to GI immaturity.

**DISCUSSION**

A large part of the morbidity associated with preterm birth is related to feed intolerance. Given that term infants rarely experience feeding difficulties, it is accepted that feed intolerance in the preterm infant is related to GI immaturity. Although various feeding trials and treatments have attempted to ameliorate feed intolerance, they have met with limited success.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of preterm infants given insulin or not (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age (weeks)</strong></td>
<td>Insulin group (n=8)</td>
</tr>
<tr>
<td>27.8 (2.5)</td>
<td>27.8 (1.2)</td>
</tr>
<tr>
<td><strong>Birth weight (g)</strong></td>
<td>973 (310)</td>
</tr>
<tr>
<td><strong>Age feeds begun (days)</strong></td>
<td>9.9 (3.1)</td>
</tr>
<tr>
<td><strong>Percentage of feeds with human milk</strong></td>
<td>30 (32)</td>
</tr>
<tr>
<td><strong>Age at lactase measurement (days)</strong></td>
<td>29 (3)</td>
</tr>
<tr>
<td><strong>Antenatal glucocorticoids (n)</strong></td>
<td>4 (50%)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Lactase activity and measures of feeding intolerance in preterm infants given insulin or not (controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactase activity</strong></td>
<td>Insulin group (n=8)</td>
</tr>
<tr>
<td>13.3 (6.7–65.4)</td>
<td>6.5 (0.43–54.76)</td>
</tr>
<tr>
<td><strong>Age at full enteral feeds (days)</strong></td>
<td>21 (6)</td>
</tr>
<tr>
<td><strong>Days to full enteral feeding</strong></td>
<td>11 (6)</td>
</tr>
<tr>
<td><strong>Mean number per infant</strong></td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Gastric residuals &gt;2 ml/kg</strong></td>
<td>2.4 (3.4)</td>
</tr>
<tr>
<td><strong>Gastric residuals &gt;50% of previous feeding</strong></td>
<td>2.3 (4)</td>
</tr>
</tbody>
</table>

Values are median (range) or mean (SD).
In vitro and in vivo work in animals documents the ability of insulin to enhance GI development and function. A growing body of literature from studies in various animal species supports the earlier observation in newborn pigs that administration of enteral insulin also accelerates GI development. Insulin is attractive as an agent to enhance GI development in the preterm infant. It is normally present in human milk at high concentrations relative to maternal blood. It is not absorbed systemically to any significant degree as measured by changes in blood sugar in this study and in a previous investigation. It is inexpensive and readily available.

The results of this study suggest that enteral administration of insulin to preterm infants enhances GI function, as measured by increased lactase activity (table 2; fig 1). Previous studies have documented the importance of lactase activity and lactose digestibility in reducing feed intolerance in preterm infants: randomized trial of gastrointestinal priming and tube-feeding. However, the mechanism of this increase is not clear. The outlier in lactase activity in both groups (fig 1) is not clear. The outlier in the insulin group was re-measured at 40 days of age and the value was even higher, suggesting that the value at 28 days of age was not an error. Presumably, this variation in lactase activity in both groups reflects the variability in intestinal maturation among infants. It may explain, in part, why different infants follow such diverse clinical courses.

A limitation of this preliminary study is the retrospective nature of the control infants. However, management of the insulin treated and control infants was similar as it was controlled by nursery protocol. Further, the investigator had no input into the management of any infants as this was in the hands of the various attending neonatologists. Recent studies have documented the value of similar case-controlled investigations.

The goal of this study was to ascertain whether there was evidence that insulin is efficacious in enhancing GI development and reducing feed intolerance in preterm infants. Given that these pilot data support this hypothesis, I suggest that a randomised, placebo controlled trial is indicated. Although I observed no ill effects during the course of insulin administration or throughout the remainder of the hospital stay, potential long term effects such as the development of insulin antibodies or the prevention of diabetes (as has been observed in animal models) must be explored in future trials. Although previous studies suggested that hypoglycaemia was unlikely to occur, a much larger number of infants would need to be studied to exclude the possibility. Therefore enteral insulin should not be used outside of a study setting.

ACKNOWLEDGEMENTS

This study was supported by the Daffy's Foundation and the USDA/ARS under Cooperative Agreement No 58-6250-1-003. This work is a publication of the USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX. The contents of this publication do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organisations imply endorsement by the US Government.

REFERENCES