Insulin and Growth-Hormone Responses in Neonatal Hyperglycemia

Mehru Zarif, M.D., Rosita S. Pildes, M.D., and D. Vidyasagar, M.D.,
Chicago

SUMMARY

Glucose, insulin, and growth hormone values were studied prospectively in 75 premature infants during the first five days after birth. Intravenous glucose was given at a mean rate of 4.7-4.9 mg./kg./ min. (range 3-7). Mean birth weight was 1,394 ± 47 gm. (mean ± S.E.M.). Blood glucose values were significantly higher on days 1 and 2 than on days 3 to 5. Hypoglycemia (blood glucose <20 mg./100 ml.) occurred in two SGA and one AGA infants. On the other hand, hyperglycemia (>125 mg./100 ml.) was found in 32 of the 75 (42.7 per cent) infants. A significantly greater number of deaths occurred in infants with hyperglycemia (19/32) than in those with normoglycemia (5/43). Mean plasma insulin values were significantly higher on days 1 and 2 (15 ± 3 and 18 ± 4 μU./ml.) than on days 3 and 4-5 (6 ± 1 and 7 ±2 μU./ml.). In addition, mean insulin levels were significantly higher during hyperglycemic than during normoglycemic glucose levels at similar postnatal age. Growth hormone values were higher during the first three days than subsequently, but the values were similar in normoglycemic and hyperglycemic groups. Significant negative correlations were seen between glucose values on the first two days of postnatal life and birth weight, gestational age, and Apgar scores, whereas positive correlations were found with FiO_2 and respiratory distress score (RDS). DIABETES 25:428-33, May, 1976.

Parenteral glucose infusions have been widely used in the neonatal period to provide supplemental calories, treat hypoglycemia[1] and respiratory distress syndrome,[2-3] and improve survival of infants weighing less than 1,250 gm. at birth.[4] In general, intravenous infusions of glucose have been well tolerated, although hypoglycemia has been found when hypertonic solutions were discontinued abruptly.[1] Hyperglycemia (>150 mg./100 ml.) has been reported in infants of less than 1,300 gm. at birth who were given supplemental parenteral nutrition in the form of 10 per cent dextrose and casein hydrolysate[5] and in a retrospective analysis of 50 infants of less than 1,100 gm. at birth.[6] Impaired glucose utilization on the basis of a diminished insulin response to parenteral glucose was postulated as a possible contributing factor;[16] insulin levels, however, were not measured.

The purpose of this study was to assay prospectively glucose, insulin, and growth hormone response of low-birth-weight infants who were given intravenous or oral fluids from the first day of postnatal life. The role of insulin and growth hormone in the pathogenesis of neonatal hyperglycemia was studied. Attempts were made to correlate blood glucose values with clinical assessments of gestational age, birth weight, Apgar scores, and respiratory distress as well as with blood gases, bilirubin, hematocrit, and total protein.

METHODS AND MATERIALS

Seventy-five infants who weighed between 567 and 2,000 gm. (mean ± S.E., 1,376 ± 48 gm.) at birth were studied prospectively from December 1972 to May 1973. There were 61 black and 14 white infants. Forty-six (61 per cent) were male and 29 (39 per cent) female. No reason for this discrepancy could be found. Sixty were less than 24 hours old and 15 between 24 and 36 hours of age at the time they were entered into the study. Gestational age was estimated from mater-

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From the Departments of Pediatrics, Cook County Hospital and University of Illinois College of Medicine, and the Hektoen Institute, Chicago.

Address reprint requests to Rosita S. Pildes, M.D., 700 South Wood Street, Chicago, Illinois 60612.

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nal history of last menstrual period and clinical assessment. If the two differed by more than two weeks, the infant was not included in the study. Gestational ages ranged from 29 to 36 weeks (mean, 30.9 ± 0.4). There were 11 (14.6 per cent) small for gestational age and three (4.6 per cent) large for gestational-age infants. One-minute Apgar score was available in 70 infants; 29 were rated between 7 to 10, 27 at 3 to 7, and 14 at <3.

All the infants were born at Cook County Hospital and transferred from the delivery rooms to the neonatal intensive-care unit. The only infants included in the study were those who required intravenous fluids or repeated biochemical determinations. None of the infants had sepsis, but respiratory distress syndrome and birth asphyxia were common. The infants were placed in isolettes, and their temperature was maintained within the neutral thermal range for weight and gestational age. Respiratory distress was graded on the basis of the RDS score.[7] Umbilical-artery catheters were placed at the level of L2-L3 in any infant who required measurements of blood gases. Intravenous fluids were started in all infants who weighed <1,250 gm. and in those who had respiratory distress or low Apgar scores that were still depressed at time of transfer. Fluids were given at the usually recommended rate and concentration, depending on weight and age of the infant. Fluids were started before six hours of age and infused by means of infusion pumps at a rate of 60-70 ml./kg./day during the first day of life, and this was gradually increased over the next five days. In general, 10 per cent dextrose and water was given for the first 24-48 hours, and this was subsequently changed to 5 per cent dextrose and 0.2 N saline. The rate of glucose infusion is shown in table 1. Oral feedings were given as soon as tolerated, beginning with two sterile water feedings and switched to a 20-cal./oz. formula if sterile water was well tolerated. Only four of the 75 infants received only formula feedings during the first 24 hours. The amount of glucose or carbohydrate intake in the oral feedings was not included in the calculation of quantity of glucose infused/kg./min.

Biochemical determinations were made as frequently as necessary for the individual neonate. However, all specimens taken between 8:00 A.M. and 10:00 A.M. were drawn by one of us in order to avoid technical errors. Oral feedings were withheld for three to three and one half hours prior to blood drawing. Warmed arterialized[8] heel stick blood was used for measurements of blood glucose in order to avoid contamination from the infusion catheter.[9] Heel stick blood was also used for measurements of hematocrit, serum bilirubin, and total protein. An additional 1 ml. blood was drawn simultaneously into heparinized tubes from the umbilical arterial catheter. A portion of this blood was used for blood gas analysis, and the remainder was immediately spun down at −4° C. and stored at −20° C. Blood glucose was measured by the glucose oxidase method.[10] Plasma insulin and growth hormone were measured by radioimmunoassay using a modification of the charcoal technic of Herbert et al.[11] Serum protein and bilirubins were assayed in the routine microlaboratory of the Hektoen Institute. Infants who developed severe hyperglycemia were treated by lowering the glucose concentration in the infusate, which partly accounts for the range, 3-7 mg./kg./min., of glucose infused. None of the infants received insulin and, hence, all continued to be monitored and included in the data.

Samples obtained during the first five days were included for analyses. Although some infants had more than one sample drawn during the day, the A.M. blood sample was the only one used for the study. Two types of data analysis were performed. The first consisted of entering all variables into a 62 × 62 correlation matrix, each correlation coefficient being tested for significance (Student's *t*-test).[12] The second analysis was a stepwise discriminant-function analysis on selected clinical variables.[13] Data during the first 24 hours were grouped together and considered day 1. Data from days 4 and 5 were grouped together in order to increase the sample size after statistical analysis to ensure that there were no differences between these two days.

RESULTS

Clinical Characteristics

The rate of glucose infusion remained relatively constant over the five days, with a mean rate of 4.7 ± 0.1 mg./kg./min. (range 3-7 mg./kg./min.) on the first day (table 1). Calories given increased progressively from 28 ± 2 cal./kg. on the first day of life to 66 ± 5 cal./kg. on the fourth and fifth days. Total fluid intake (oral ± I.V.) increased from 66 ± 2 ml./kg. on the first day to 131 ± 6 ml./kg. on the fifth day.

Blood Glucose

Two hundred and twenty-one blood glucose values, or 2.9 samples per patient, were done on the 75 infants during the first five days of age. Blood glucose

TABLE 1

Rates of intravenous infusions, total calories, capillary blood glucose, plasma insulin, insulin-to-glucose ratio, and plasma growth hormone during the first five days of age (mean ± S.E.M.). Numbers in parentheses indicate number of determinations

Age	I.V. fluids glucose mg./kg./min.	Total calories/kg./day I.V. + oral	Glucose mg./100 ml.	Insulin μU./ml.	Insulin: glucose ratio	Human growth hormone ng./ml.
Day 1	4.7 ± 0.12	28.4 ± 1.9	124.7 ± 19.0 (61)	14.6 ± 3.1 (49)	0.18 ± 0.04	73.7 ± 4.5 (49)
Day 2	4.7 ± 0.19	45.5 ± 3.8	94.2 ± 13.3 (63)	17.8 ± 4.0 (35)	0.24 ± 0.08	70.1 ± 5.3 (29)
Day 3	4.9 ± 0.31	58.9 ± 4.8	64.1 ± 5.1 (44)	5.8 ± 1.3 (21)	0.13 ± 0.04	71.1 ± 5.9 (19)
Days 4 & 5	4.8 ± 0.41	65.9 ± 5.2	66.6 ± 5.1 (53)	5.8 ± 1.8 (26)	0.14 ± 0.03	58.5 ± 5.7 (25)

values (mean ± S.E.) during the first 24 hours were not significantly different from those on the second day. However, the values were significantly higher ($p < 0.01$) on day 1 than on days 3 to 5. Glucose values were significantly higher ($p < 0.05$) on day 2 than on day 3, but the differences were not significant subsequently (table 1).

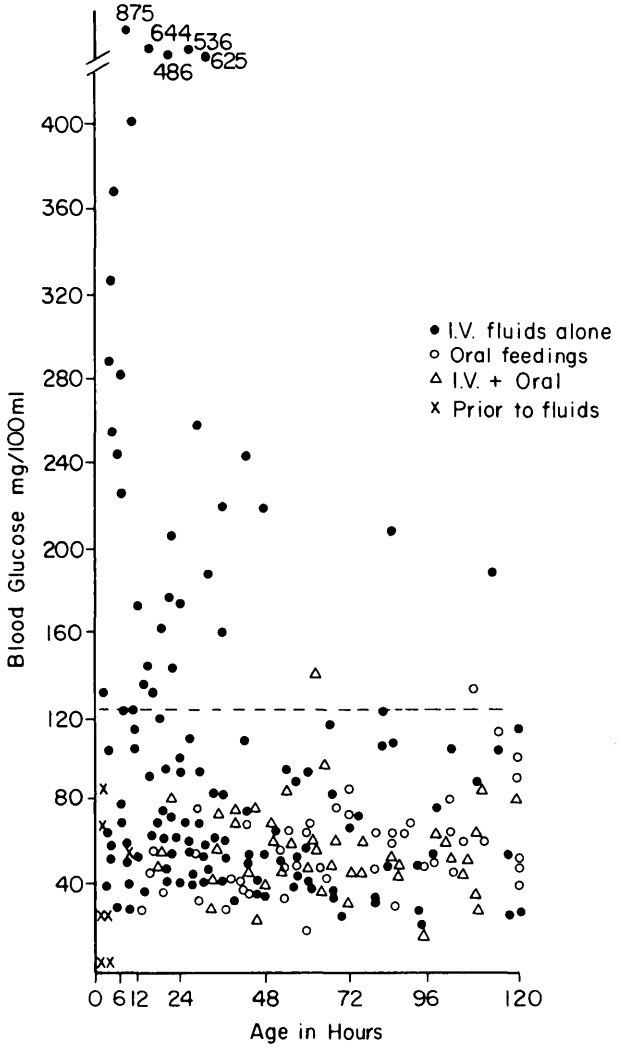

FIG. 1. Individual glucose values during the first five days of postnatal life.

Individual glucose values are shown in figure 1. Hypoglycemia, determined from blood glucose values of <20 mg./100 ml.[1] was found in three infants, 2 SGA and 1 AGA, an incidence of 4.0 per cent. Hyperglycemia, from blood glucose values of >125 mg./100 ml., was observed in 32 of the 75 infants, an incidence of 42.7 per cent. Those values ranged up to 875 mg./100 ml. All but two of the 32 infants were getting solely intravenous glucose infusions at the time of testing. Hyperglycemia was found in two of the 11 SGA and 1 of the 3 SGA infants. The degree of hyperglycemia diminished with increasing postnatal age.

Plasma Insulin and Growth Hormone

Plasma insulin values (table 1) were similar on the first and second days of life. Both values were significantly higher ($p < 0.01$) than values on day 3 and days 4 and 5. Insulin-to-glucose ratios were not significantly different during day 1 and 2 from during days 3, 4, and 5. Mean insulin value was significantly ($p < 0.01$) higher (22.6 ± 4.6 μU./ml.) at the time of hyperglycemia than in the normoglycemic infants (10.7 ± 1.8 μU./ml.). Mean insulin values in severe hyperglycemia (above 200 mg./100 ml.) were 29 ± 3.7 μU./ml., whereas in moderate hyperglycemia (above 125 and below 200 mg./100 ml.) the values were 15.2 ± 5.8 μU./ml. The insulin-to-glucose ratio was similar in both moderate and severely hyperglycemic prematures. A wide variation in responses was seen, with insulin values ranging from 2 μU./ml. in one neonate with a blood glucose of 625 mg./100 ml. to 85 μU./ml. in another with a reading of 258 mg./100 ml.

Growth hormone values (table 1) showed great variation among individual infants. Mean growth hormone values were high during the first three days of life and became significantly lower on days 4 and 5. There were no significant differences in HGH whether glucose values were <125 mg./100 ml. or >125 mg./100 ml.

TABLE 2

Correlations between glucose values on days 1-5 and clinical variables. Glucose, FiO_2, and RDS score are of corresponding days

	Day 1		Day 2		Day 3		Days 4 & 5	
Variable	r*	P	r*	P	r*	P	r*	P
Gestational age	−0.45	<0.001	−0.33	<0.05	−1.9	N.S.	−0.219	N.S.
Birth weight	−0.33	<0.05	−0.34	<0.01	−0.27	N.S.	−0.186	N.S.
Apgar score	−0.26	<0.05	−0.35	<0.01	−0.12	N.S.	−0.004	N.S.
FiO_2	0.67	<0.001	−0.47	<0.001	−0.017	N.S.	−0.050	N.S.
RDS score	0.61	<0.001	−0.57	<0.001	−0.028	N.S.	−0.201	N.S.

*Pearson Correlation Coefficient.

RDS Score and Blood Gas Analysis

The mean RDS score was significantly higher ($p < 0.01$) on day 1 (3.7 ± 0.3) and day 2 (2.5 ± 0.8) than on subsequent days (1.5 ± 0.4 and 1.1 ± 0.4). The infants were often mildly acidotic (pH 7.28 ± 0.02) on the first day and required a significantly ($p < 0.01$) higher FiO_2 on day 1 (47 ± 3.4 per cent) than on subsequent days (29 ± 3 per cent on days 4 + 5) in order to maintain pO_2 values between 50 and 100 mm. Hg.

Mean bilirubin values were 7.2 ± 0.4 between 24 and 48 hours of life and reached a peak of 10.8 ± 0.55 mg. per cent on the fourth and fifth day.

Hematocrit values were significantly higher during the first day (55.7 ± 0.3 per cent) than on subsequent days and dropped to 45.1 ± 1.1 per cent by the third and fourth days of life. Total protein values rose from 4.7 ± 0.17 gm. per cent to 5.2 ± 0.84 gm. per cent, but the differences were not significant.

Clinical and Biochemical Correlations

Significant negative correlations were found between blood glucose and gestational age, birth weight, and Apgar score during the first two days of postnatal age. In addition, significant positive correlations were seen between glucose and inspired oxygen concentration or RDS score. These correlations were no longer significant on days 3 and 4 (table 2). There was no correlation between glucose values and the rate of glucose infusion in mg./kg./min. or between glucose values and total caloric intake in cal./kg./day.

Blood glucose values were also correlated with levels of blood gases, bilirubin, hematrocrit, and total protein. A significant negative correlation ($r = -.71$, $p < 0.001$) was seen with pH on day 1, but, as acidosis was rapidly corrected, these correlations were not subsequently significant. There were no significant correlations between glucose values and the other biochemical data or in glucose values and insulin and growth hormone values. There were no significant correlations between insulin or growth hormone values and the clinical variables.

Comparison of the clinical data in the normoglycemic versus the hyperglycemic group of infants (table 3) further confirmed the correlation studies. Hyperglycemic infants were of significantly lower birth weight and gestational age and had significantly lower mean Apgar scores and higher RDS score.

TABLE 3

Clinical characteristics of infants with blood glucose >125 mg./100 ml. (hyperglycemic) vs. blood glucose <125 mg./100 ml. (normoglycemic)

	Hyperglycemic group	Normoglycemic group
Birth weight (gm.)	1,185 ± 61.0*	1,539 ± 57.7 (S.E.)
Gestation (wk.)	28.7 ± 0.55*	32.5 ± 0.5
Apgar scores		
Mean	4.8 ± 0.5†	6.2 ± 0.4
7-10	9	20
3-6	13	14
<3	9	5
RDS score		
Mean	5.9 ± 0.6*	2.5 ± 0.4
7-10	13	3
3-6	11	13
<3	8	27

*p <0.001
†p <0.05
Mean ± S.E.M.

Using the significant clinical variables shown in table 2, we performed a stepwise discriminant function analysis[13] in an attempt to predict whether an infant would belong to the higher glucose group (>125 mg./100 ml.) or the low glucose group (<125 mg./100 ml.). This was not successful, since a great deal of overlap was found between the groups. Thus, the clinical variables, although significantly correlated with blood glucose values, could not be used to predict the glucose values of an individual infant.

Mortality. Of the 32 infants with hyperglycemia, 19 died. In contrast, only five of the 43 normoglycemic infants died. This difference was highly significant, $\chi^2 = 19.1$, $p < 0.001$.

Autopsies were available in 18 of the 19 hyperglycemic and in four of the five normoglycemic new-

borns who died. Intracranial hemorrhage was present in a similar proportion of infants (10/18) who had blood glucose values >125 mg./100 ml. as in those with values <125 mg./100 ml. (2/4). Hyaline membrane disease, pulmonary hemorrhage, or atelectasis was found in 13 of 18 in the hyperglycemic and three of four in the normoglycemic group. One infant in each group died secondary to surgical problems: ruptured stomach in one and duodenal atresia in the other.

DISCUSSION

Neonatal hyperglycemia has been generally associated with the clinical syndrome of congenital transient diabetes mellitus, which may persist for weeks or months.[14] A more temporary hyperglycemia, lasting only 24 hours, has been reported in isolated cases.[15] Until recently, however, hyperglycemia that developed during administration of intravenous fluids was not given much significance. It is apparent from this study and from observations of other investigators[5,6] that hyperglycemia is a significant finding in low-birth-weight infants. The definition of hyperglycemia in the neonatal period has been the presence of glucose values greater than 125 mg./100 ml.[1] These studies, however, did not include measurements of glucose values in those infants who were receiving parenteral glucose. Using this criterion, 42.7 per cent of the infants in our study developed hyperglycemia during parenteral glucose therapy. Dweck and Cassidy[6] reported an 86 per cent incidence of hyperglycemia in infants who weighed less than 1,100 gm. at birth and who were given higher rates of glucose infusion than in the present study.

The pathogenetic mechanisms for the development of hyperglycemia remain obscure. Significantly higher insulin values were observed during the first two days of age, when glucose values were very high. Insulin values were also higher in neonates whose glucose values were above 200 mg./100 ml. In addition, insulin-to-glucose ratios were not significantly different during the first two days than on subsequent days, thus indicating an appropriate response. It may be argued that insulin secretion was inappropriately low since, in fact, the infants were hyperglycemic. This could occur if there was a lag in B-cell response to the hyperglycemic stimulus similar to that observed in adult-onset diabetes; ultimately, the continuing hyperglycemia results in hyperinsulinemia. This hypothesis can not be proved with our studies since only isolated insulin values were obtained. Diminished insulin responses to acute glucose loads in low-birth-weight infants have been reported.[16,17] On the other hand, Gentz et al. concluded that insulin responses as measured in peripheral plasma were extremely variable in infants <1,500 gm. and could not be used to explain the rate of removal of glucose from their plasma. In this study, variability of responses was also apparent in that insulin values during hyperglycemia ranged from 2 to 85 μU./ml. However, mean insulin values were significantly higher than during normoglycemia. Phelps and Oh also reported appropriate serum insulin levels during constant glucose infusion.[19]

Growth hormone values obtained during the first three days of life were elevated. It would be interesting to postulate that the high growth hormone values may have resulted in the glucose intolerance. Several factors militate against this conclusion. First, growth hormone values are known to be high during the first days of life even in infants who are not hyperglycemic or receiving glucose infusions.[20,21] Second, growth hormone responses to acute intravenous glucose loads in neonates are frequently parodoxical, showing a rise rather than a fall.[20] Thus, the high values could have been secondary to the glucose infusions. Finally, growth hormone values were similar when examined in infants who had high glucose values as compared with those of normals.

From this study, neither inadequate insulin nor excessive growth hormone responses could be incriminated as significant etiologic factors in the glucose intolerance exhibited by these small premature infants. Since many of these infants have suffered significant stress, it is possible that increased cortisol or catecholamine secretion are important contributing factors. Cortisol was not measured, but indirect evidence of its possible increase has been shown by the observation of high cortisol values in premature infants with hyaline membrane disease.[22] In addition, circulating blood volume may have been limited in these distressed infants, leading to inadequate perfusion of glucose-sensitive tissues. Finally, variability of infusion rates may have occurred in spite of infusion pumps.

Hyperglycemia, by virtue of increasing serum osmolality, might cause dehydration of brain cells and subsequent cerebral hemorrhage and death.[23] We were unable to confirm this hypothesis from analyses of autopsy findings in the infants in this study, but a larger series of normoglycemic infants needs to be

included before hyperglycemia as a cause of cerebral hemorrhage can be excluded. Finberg suggested that an increase in 25 to 40 mOsm is associated with intracranial hemorrhage. This would require a blood glucose value of greater than 400 mg./100 ml. Five of the infants in this study had blood glucose values that ranged between 486 and 875 mg./100 ml., and two of the five had intracranial hemorrhages. Others, however, have found an increased incidence[6] of cerebral hemorrhage in neonatal hyperglycemia.

Correlations between glucose values and clinical data indicated that hyperglycemia was seen in the smaller, more critically ill infants in spite of apparently low rates of glucose infusions. Since hyperglycemia may result in osmotic diuresis, hyponatremia, and weight loss, an additional risk factor may have been present in these highly precarious infants, leading to an increased mortality. Blood glucose values should, therefore, be monitored frequently in small neonates who are receiving glucose intravenously. Glucose concentration in the infusate or rate of glucose infusion should be decreased if hyperglycemia is found. The long-term effects of hyperglycemia in surviving infants are unknown. Until they are determined, one could hardly quarrel with the recommendation that blood glucose concentrations be kept as normal as possible.

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