Intravenous Glucose Tolerance and Plasma Insulin Studies in Small-for-dates Infants

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Le Dune, M. A. (1972). *Archives of Disease in Childhood*, 47, 111. **Intravenous glucose tolerance and plasma insulin studies in small-for-dates infants.** A study of infants who were small-for-dates is described. A proportion of them developed hypoglycaemia, and in these, intravenously administered glucose disappeared abnormally rapidly from the blood, shown by a raised kG value. Some of these infants also showed raised levels of plasma insulin. Those with the high levels of plasma insulin showed significant change in fasting 'true' blood glucose, and mean maximum plasma insulin levels at the end of the first week of life. Hypoglycaemia of the newborn is probably more closely related to other factors as yet still undefined, than to changes in plasma insulin alone.

The carbohydrate metabolism of the infant who is small for his gestational age is known to be unstable. Hypoglycaemia may arise (Cornblath and Schwartz, 1966), and also occasionally transient neonatal diabetes (Gentz and Cornblath, 1969). The reasons for this instability have not been fully explained.

Gentz, Persson, and Zetterström (1969a) showed that in infants with symptomatic hypoglycaemia, intravenously administered glucose disappeared very quickly from the blood. Cornblath *et al.* (1966) showed that relatively high levels of plasma insulin were present in infants with symptomatic hypoglycaemia as compared with asymptomatic controls.

This paper is an attempt to investigate the cause of the hypoglycaemia by using the injection of 50% glucose usually employed therapeutically as an intravenous glucose tolerance test, and to estimate serially the plasma insulin.

Material

A total of 48 infants has been studied. All were born either in the Queen Mother's Hospital, Stobhill General Hospital, or Robroyston Hospital, Glasgow. Infants who were below the 5th centile in weight on the Aberdeen intrauterine growth chart of Tanner and Thomson (1970), before correction was made for maternal stature, were included in this series. A faint or zero recording with the Dextrostix test paper within 6 hours of birth had also to be obtained. Twins and

singletons with congenital abnormalities or hypothermia were all excluded.

Procedure

All intravenous glucose tolerance tests were carried out between the fourth and sixth hours of life, except in 4 cases where the initial Dextrostix gave a zero reading, and even earlier testing was therapeutically indicated. Blood was taken by heel-prick for a fasting 'true' blood glucose and plasma insulin. An intravenous injection of 50% glucose in a dose of 1.0 g/kg was given into the smallest available peripheral vein, usually into the back of the hand. The injection was given over a period of 2 minutes. Blood was then taken again by heel-prick 5, 10, 20, 30, and 60 minutes after the injection for further estimations of 'true' blood glucose and plasma insulin. Oral feeding was not started until all the tests were completed. Intravenous glucose tolerance tests were repeated at the end of the first week of life in 11 infants where the initial 'true' blood glucose level was 20 mg/100 ml or below.

Biochemical Methods

'True' blood glucose was estimated by the glucose oxidase method of Marks (1959). The plasma immunoreactive insulin was estimated by the double-antibody method of Hales and Randle (1963). The rate of disappearance of 'true' blood glucose from the blood was expressed by the kG value (Lundbaek, 1962). This gives the percentage diminution per minute of 'true' blood glucose from the blood and was calculated from the formula $y = te^{-kt}$.

Results

Hypoglycaemia was defined as a fasting 'true' blood glucose of 20 mg/100 ml or below. On this

basis the infants were divided into two groups.

(1) *Hypoglycaemic group*: a group of 18 infants with a 'true' blood glucose of 20 mg/100 ml or below.

(2) *Nonhypoglycaemic group*: a group of 30 infants with a 'true' blood glucose of above 20 mg/100 ml.

The comparison of the intravenous glucose tolerance and plasma insulin estimations is shown in Table I. In the hypoglycaemic group the mean fasting 'true' blood glucose was lower ($P < 0.001$) and the mean fasting plasma insulin level higher ($P < 0.02$). In this group, glucose disappeared much more quickly from the blood, as shown by a raised kG value ($P < 0.001$).

As an expression of insulin secretion in response to the glucose load, the maximum plasma insulin level was taken for each patient whenever it occurred during the 60-minute test period (Fig.). In the hypoglycaemic group the mean maximum plasma insulin level was raised ($P < 0.025$). The highest insulin level recorded among the 30 nonhypoglycaemic cases was taken as 35 $\mu\text{U/ml}$. On this basis the hypoglycaemic group was divided further into those showing a *high* insulin response, $> 35 \mu\text{U/ml}$, and those showing a *normal* insulin response below this level.

FIG.—Maximum plasma immunoreactive insulin levels in response to glucose load in 30 nonhypoglycaemic infants (unhatched blocks); and 18 hypoglycaemic infants (hatched blocks), of whom 6 gave high insulin responses ($> 35 \mu\text{U/ml}$).

Eleven patients in the hypoglycaemic group were followed up with repeat intravenous glucose tolerance tests at the end of the first week of life. Comparison is made in Table II of the intravenous glucose tolerance and plasma insulin estimations, before and after treatment at the end of the first week of life. In the treated infants there was significant change in the fasting 'true' blood

TABLE I

Comparison of the Intravenous Glucose Tolerance and Plasma Insulin Estimations in Hypoglycaemic and Nonhypoglycaemic Small-for-dates Infants

Small-for-dates Infants	No.	Mean Fasting 'True' Blood Glucose (mg/100 ml) Mean $\pm$ SD (range)	Mean kG Mean $\pm$ SD (range)	Mean Fasting Plasma Insulin ($\mu\text{U/ml}$) Mean $\pm$ SD (range)	Mean Maximum Plasma Insulin ($\mu\text{U/ml}$) Mean $\pm$ SD (range)
Hypoglycaemic group	18	10.3 $\pm$ 5.2 (5–20)	2.7 $\pm$ 1.1 (1.6–5.9)	12.9 $\pm$ 9.3 (5–34)	27.2 $\pm$ 18.3 (8–68)
Nonhypoglycaemic group	30	33.9 $\pm$ 8.5 (24–55)	0.8 $\pm$ 0.2 (0.5–1.3)	8.0 $\pm$ 3.8 (5–21)	18.6 $\pm$ 8.1 (5–35)
Significance of difference		P < 0.001	P < 0.001	P < 0.02	P < 0.025

TABLE II

Comparison of the Intravenous Glucose Tolerance and Plasma Insulin Estimations in the Hypoglycaemic Small-for-dates Infants, Before and After Treatment

Small-for-dates Hypoglycaemic Infants	No.	Mean Fasting 'True' Blood Glucose (mg/100 ml) Mean $\pm$ SD (range)	Mean kG Mean $\pm$ SD (range)	Mean Fasting Plasma Insulin ($\mu\text{U/ml}$) Mean $\pm$ SD (range)	Mean Maximum Plasma Insulin ($\mu\text{U/ml}$) Mean $\pm$ SD (range)
Before treatment	18	10.3 $\pm$ 5.2 (5–19)	2.7 $\pm$ 1.1 (1.6–5.9)	12.9 $\pm$ 9.3 (5–34)	27.2 $\pm$ 18.3 (8–68)
After treatment	11	25.8 $\pm$ 11.9 (8–40)	1.7 $\pm$ 0.5 (0.9–2.6)	9.4 $\pm$ 7.9 (5–32)	18.7 $\pm$ 13.5 (8–53)
Significance of difference		P < 0.001	P < 0.02	NS	NS

TABLE III

Comparison of the Intravenous Glucose Tolerance and Plasma Insulin in a Group of Small-for-dates Infants who were Hypoglycaemic with a Normal Insulin Response, Before and After Treatment

Small-for-dates Infants with Normal Insulin Response	No.	Mean Fasting 'True' Blood Glucose (mg/100 ml) Mean $\pm$ SD (range)	Mean kG Mean $\pm$ SD (range)	Mean Fasting Plasma Insulin (μ U/ml) Mean $\pm$ SD (range)	Mean Maximum Plasma Insulin (μ U/ml) Mean $\pm$ SD (range)
Before treatment	12	11.3 $\pm$ 5.6 (5-20)	2.7 $\pm$ 1.3 (1.6-5.9)	10.3 $\pm$ 7.0 (5-28)	16.1 $\pm$ 7.8 (<5-28)
After treatment	7	26.3 $\pm$ 10.7 (12-34)	1.6 $\pm$ 0.6 (0.9-2.6)	7.9 $\pm$ 3.0 (5-12)	16.9 $\pm$ 8.6 (8-30)
Significance of difference		P < 0.001	NS	NS	NS

TABLE IV

Comparison of the Intravenous Glucose Tolerance and Plasma Insulin in a Group of Small-for-dates Infants who were Hypoglycaemic with a High Insulin Response, Before and After Treatment

Small-for-dates Infants with High Insulin Response	No.	Mean Fasting 'True' Blood Glucose (mg/100 ml) Mean $\pm$ SD (range)	Mean kG Mean $\pm$ SD (range)	Mean Fasting Plasma Insulin (μ U/ml) Mean $\pm$ SD (range)	Mean Maximum Plasma Insulin (μ U/ml) Mean $\pm$ SD (range)
Before treatment	6	8.5 $\pm$ 4.1 (5-16)	2.6 $\pm$ 0.7 (1.9-3.8)	18.2 $\pm$ 11.6 (10-34)	49.3 $\pm$ 11.1 (38-68)
After treatment	4	25.0 $\pm$ 15.4 (8-40)	1.9 $\pm$ 0.5 (1.3-2.5)	12.0 $\pm$ 13.3 (5-32)	22.0 $\pm$ 20.9 (8-53)
Significance of difference		P < 0.05	NS	NS	P < 0.025

glucose (P < 0.001) and kG value (P < 0.02) when repeat intravenous glucose tolerance tests were carried out at the end of the first week of life. There was no significant change, however, in the mean fasting or mean maximum plasma insulin levels.

The *high* and *normal* insulin response groups were considered separately before and after treatment at the end of the first week of life (see Tables III and IV). In the normal insulin response group (Table III), the mean fasting 'true' blood glucose alone showed a significant improvement (P < 0.001). On the other hand, in the high insulin response group (Table IV), significant increase was found in the mean fasting 'true' blood glucose (P < 0.05) and decrease in the mean maximum plasma insulin (P < 0.025). At the end of the first week of life, the mean fasting and mean maximum plasma insulin estimations in the high insulin response group were not significantly different from those in the normal insulin response group.

Treatment and progress. All the infants in the hypoglycaemic group were treated with intravenous glucose until they were able to maintain alone a satisfactory level of 'true' blood glucose. The

intravenous glucose was then slowly withdrawn. Two infants were given, in addition to the intravenous glucose, corticosteroid intramuscularly, since the intravenous glucose alone was unable to maintain the level of 'true' blood glucose above 20 mg/100 ml. Three infants died, none was hypoglycaemic at the time of death. This, however, probably reflects the well-recognized hazard to the infant of placental insufficiency.

Discussion

The factors that influence the removal rate of glucose from the blood are not fully understood. A high kG value may indicate that the peripheral tissues have used up the glucose so rapidly that the amount available to the brain has been reduced to a critical level. In this series it is noteworthy that the kG value was found to be raised in all the hypoglycaemic infants irrespective of whether they had normal or increased insulin secretion. The fact that some infants with hypoglycaemia had high, and some had normal, plasma insulin levels suggests that within the hypoglycaemic group there may be two distinct populations, or else these groups may represent different stages of the same disease. Low concentrations of free-fatty acids have been found

in some infants with hypoglycaemia, and Gentz *et al.* (1969b) reported in one case a drop in kG value after the administration of Intralipid. It was suggested that this drop in kG value might have been related to an increased utilization of exogenous fat. Estimations of free-fatty acids in conjunction with the insulin studies in the present series would be of particular interest. Since in the present study, the emphasis was to initiate treatment before symptoms arose, one can only speculate as to whether or not those with the high insulin levels would have been the ones to develop symptoms if left untreated.

The fact that the cause or severity of the illness does not seem to be much different in the two groups with high and normal insulin secretion suggests that the hypoglycaemia is probably more closely related to other factors as yet still undefined, than simply to changes in insulin level. The possibility also exists that some of the insulin measured in the radioimmunoassay may be inactive proinsulin.

Inadequate stores of liver glycogen may be in part the explanation for this tendency towards hypoglycaemia, as suggested by Shelley and Neligan (1966). In support of the work of Dawkins (1964), the liver size was found to be considerably reduced relative to that of the brain in the three infants who died. This is shown by the liver/brain ratio which is normally 3 : 1, but in the three infants who died the ratios were 6·3 : 1, 5·5 : 1, and 5·3 : 1, respectively. On the other hand, Blum *et al.* (1969), following their studies on the administration of intravenous glucagon to small-for-dates infants, have questioned the significance of

glycogen depletion in this condition. The matter must still be considered undecided.

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