

Therapeutic insulin and hepatic glucose-6-phosphatase activity in preterm infants

A Burchell, A McGeechan, R Hume

Abstract

Background—Hepatic glucose-6-phosphatase activity is low at birth, and in term infants rises rapidly to adult levels. In contrast, in most preterm infants, it remains low postnatally making them vulnerable to repeated hypoglycaemic episodes, resultant cerebral damage, or risk of sudden and unexpected death.

Aims—To investigate the clinical features of preterm infants with low glucose-6-phosphatase enzyme activity to determine the influencing factors.

Methods—Clinical data from 36 preterm infants were correlated by stepwise multiple regression analysis with V_{\max} of hepatic glucose-6-phosphatase as the dependent variable.

Results—The most significant correlation was with the administration of insulin (units/kg/h postnatal life) with lesser effects of respiratory distress syndrome and dopamine administration. The V_{\max} changes reflected changes in the level of expression of the glucose-6-phosphatase protein.

Conclusion—In a variety of animal models, hepatic glucose-6-phosphatase levels have been shown to decrease in response to insulin, which also decreases transcription of the glucose-6-phosphatase gene. The association of insulin administration with high levels of hepatic glucose-6-phosphatase activity and protein expression was therefore most unexpected. Results from model systems, or adults, must be extrapolated to the metabolism of preterm infants with caution.

(Arch Dis Child Fetal Neonatal Ed 2000;82:F228-F232)

Keywords: preterm; glucose; insulin; glucose-6-phosphatase

Preterm infants are vulnerable to hypoglycaemia in the neonatal period, which has long term effects on brain growth and psychomotor development.^{1,2} We have recently shown that some preterm infants (18%) at the time of discharge home have problems maintaining glucose levels if a feed is omitted or delayed.³ In the early postnatal period, preterm infants have a near constant supply of energy, but as feeding becomes more intermittent, the infant must rely on hepatic glucose production to maintain normal blood glucose levels.³

The liver has an important role in the regulation of blood glucose levels, and glucose can be made in the liver by either glycogenolysis or gluconeogenesis.⁴ Microsomal glucose-6-

phosphatase catalyses the terminal step of both glycogenolysis and gluconeogenesis.^{4,5} The importance of glucose-6-phosphatase in the regulation of blood glucose levels first became obvious in the 1950s when the debilitating effects of the complete absence of the enzyme in type Ia glycogen storage disease was first shown (see Chen and Burchell⁶ for a review). Hepatic microsomal glucose-6-phosphatase is a multicomponent system.⁴ The catalytic subunit of the glucose-6-phosphatase enzyme is situated on the luminal side of the endoplasmic reticulum membrane where it is associated with substrate and product transport proteins.⁷

In streptozotocin induced diabetes and animal models of diabetes mellitus, hepatic glucose-6-phosphatase enzyme activity, protein, and mRNA are increased about fourfold.^{8,9} Glucose-6-phosphatase activity is decreased by insulin in the normal and diabetic states in animal studies.^{10,11} More recently, the transcription of the human glucose-6-phosphatase gene has been shown to be down-regulated by insulin,¹² and upregulated to a lesser extent by glucose,¹³ but little is known of the in vivo regulation of human hepatic glucose-6-phosphatase.

We have previously shown that hepatic glucose-6-phosphatase activity in humans is low before birth,¹⁴ and in term infants it rises rapidly to adult values after delivery,¹⁴ but the factors controlling the change in postnatal expression in humans are not known. However, we have shown that, in most preterm infants, hepatic glucose-6-phosphatase activity remains low and can remain so for several months.¹⁵ Delayed postnatal appearance of hepatic glucose-6-phosphatase in preterm infants makes them vulnerable to repeated hypoglycaemic episodes and the resultant cerebral damage, or risk of sudden and unexpected death.^{1,2,16-18} We have therefore investigated the clinical features of preterm infants with low glucose-6-phosphatase activity to determine the influencing factors.

Subjects and methods

SUBJECTS

The preterm infants in this study were cared for in the same neonatal intensive care unit and died in the first five postnatal days from immature pulmonary function or intraventricular haemorrhage. The mean interval between the time when life was pronounced extinct and the time of necropsy was six hours (range 2–10 hours) during which time the bodies had been refrigerated. Fresh (non-frozen) liver samples obtained at postmortem examination were subjected immediately to subcellular fractionation

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Accepted 14 September 1999

(see below). Infants with chromosomal abnormalities, inherited metabolic defects, or early onset bacterial infection were excluded, as these conditions are associated with a variety of derangements in metabolism. Hepatic post-mortem and biopsy samples from term infants after 37–42 weeks gestation ($n = 20$), whose glucose-6-phosphatase activity was previously shown to be in the normal range,¹⁴ were used as control values in the study.

The basic characteristics of the study group were as follows: total infant number 36; ratio of boys to girls 15:21; mean (SD) gestation 27.5 (3) weeks, range 24–36 weeks; mean (SD) birth weight 1070 (461) g, range 600–2555 g. All infants had intensive care support including intermittent positive ventilation and, where appropriate, correction of fluid, electrolyte, blood glucose, and acid-base abnormalities. Blood pressure was supported with inotropes, plasma, or other blood products. Clinical and radiological features of respiratory distress syndrome were present in 29 infants with the complication of pneumothorax in 17 and pulmonary haemorrhage in nine. Intraventricular haemorrhage was present in 19 infants including eight with parenchymal haemorrhage. Renal dysfunction was common, with low urinary output (< 0.5 ml/kg/h) or elevated plasma creatinine levels in 17 infants and hyperkalaemia requiring treatment (plasma potassium > 6.5 mmol/l) in 13. The hyperkalaemia regimen consisted of the correction of acid-base disorders and hyponatraemia, if either present, and the prescription of 10% calcium gluconate (1 ml/kg every four hours intravenously) and calcium resonium resin (500 mg every six hours per rectum). For additional hyperkalaemic control, 12 of the infants required insulin and glucose (insulin 0.1–0.2 units/kg subcutaneously and glucose 50 mg/kg intravenously every four hours). In addition, two infants were prescribed insulin (0.1–0.2 units/kg subcutaneously when required) for control of hyperglycaemia (blood glucose > 10 mmol/l with glycosuria and diuresis).

The following information was collected for each preterm infant: maternal general health; health in pregnancy; disorders of pregnancy; antenatal prescribed drugs including dosage and duration; details of labour; condition of infant at birth; fetal growth parameters; postnatal disorders including respiratory distress syndrome and persistent ductus arteriosus; infective episodes; intraventricular haemorrhage; renal function; blood glucose homeostasis including initial blood glucose and subsequent highest and lowest values; time of first dose of insulin; insulin dosage; total insulin administered; insulin dose (units/kg/h postnatal life); prescribed drugs including dosage and duration—for example, dopamine; fluid and nutritional intakes.

Informed consent was obtained from parents, and the study was approved by the paediatric/reproductive medicine ethics of medical research subcommittee of Lothian Health Board.

ANALYTICAL METHODS

Preparation and assays of microsomal fractions

Liver microsomes were prepared as previously described.¹⁹ Glucose-6-phosphatase activity with glucose 6-phosphate (range 0.5–30 mM) and mannose 6-phosphate (1 mM) as substrates was measured as previously described¹⁹ and expressed as nmol/min/mg microsomal protein. Non-specific hydrolysis of glucose 6-phosphate was assayed and corrected for as previously described.¹⁹ Microsomal intactness was measured using mannose-6-phosphatase activity.¹⁹ All V_{\max} and K_m values given in this paper were calculated using a BBC computer program of non-linear multiple regression analysis.²⁰ Microsomes isolated from liver homogenates (untreated microsomes) are a mixture of intact and disrupted structures. The proportion of intact microsomes was determined in all preparations by assay of low K_m mannose-6-phosphatase activity which is only expressed in disrupted structures.²¹ All of the microsomal preparations used in this study were more than 90% intact. We have previously shown that, in microsomal preparations, which are more than 75% intact, no significant proteolysis of endoplasmic reticulum proteins occurred, nor was there any significant loss of glucose-6-phosphatase activity.¹⁷ Protein concentrations were estimated as described previously.¹⁹

Immunoblot analysis

Sodium dodecyl sulphate (SDS)/polyacrylamide gel electrophoresis was carried out on 7–16% gels, and proteins separated on SDS/polyacrylamide gels were electrophoretically transferred to nitrocellulose as described previously.^{14 22} The Western blots were immunostained with sheep IgG previously shown to be monospecific for the glucose-6-phosphatase enzyme.^{14 22} Immunoreactive peptides were made visible by the biotin/streptavidin peroxidase linked detection system with 4-chloro-1-naphthol as the substrate.

STATISTICAL ANALYSIS

Stepwise multiple linear regression was performed with V_{\max} of glucose-6-phosphatase as the dependent variable, with a cut off of probability of $F < 0.01$ significance using the SPSS for Windows version 6.1 (table 1). The p values for glucose-6-phosphatase V_{\max} and K_m (tables 2 and 3) were calculated with Student's t test using the Instat program for Macintosh computers, and the data were not adjusted for confounding variables.

Results

Stepwise multiple regression analysis as indicated in Methods, with V_{\max} of the hepatic microsomal glucose-6-phosphatase enzyme as the dependent variable, was carried out with data from 36 preterm infants. We increased the cut off of significance to 0.01 because of the large number of independent variables; insulin (units/kg/h postnatal life $\times 10^3$), respiratory distress syndrome, and dopamine ($\mu\text{g}/\text{kg}/\text{h}$ postnatal life) were the only significant results (table 1).

Table 1 Significant variables correlating with V_{max} of hepatic glucose-6-phosphatase activity

	Regression coefficient (SE)	Significance of <i>t</i>
Insulin	0.004 (0.001)	0.0002
RDS	0.077 (0.023)	0.0025
Dopamine	-0.062 (0.022)	0.0091

Insulin measured in units/kg/h postnatal life $\times 10^3$, and dopamine in $\mu\text{g/kg/h}$ postnatal life. RDS, respiratory distress syndrome.

Hepatic microsomal glucose-6-phosphatase activity (V_{max}) in preterm infants was lower than in term infants as previously reported¹⁵ (table 2). When the study group was divided into infants with and without insulin treatment, glucose-6-phosphatase activity remained low in those without insulin, whereas in those treated with insulin it was significantly higher (twofold). In contrast the K_m for the glucose-6-phosphatase enzyme did not change (table 2). When the study group was divided into infants with and without respiratory distress syndrome, those with respiratory distress syndrome had 2.5-fold higher glucose-6-phosphatase activity than those without. Again the K_m for glucose-6-phosphatase did not change (table 2). When the study group was divided into infants with and without dopamine treatment, those treated with dopamine had a lower glucose-6-phosphatase activity, although this was not quite statistically significant (significance $p = 0.05$; table 2). Changes in V_{max} of the glucose-6-phosphatase enzyme reported in this paper reflect changes in the level of expression of glucose-6-phosphatase protein, as judged by SCAN analysis of Western immunoblots.

The insulin treated infants were further divided into groups receiving low, medium, and high levels of total insulin postnatally (units/kg/h postnatal life $\times 10^3$) (table 3). Those receiving the most insulin clearly had the highest glucose-6-phosphatase activity (table 3).

Discussion

The fetus receives a constant supply of glucose across the placenta and this largely determines fetal blood glucose concentrations.²³ Hepatic glycogen accumulates during late gestation, and mobilisation of this reserve is the principal source of glucose for the first few hours of postnatal life in term infants.²⁴ At delivery, the constant transplacental supply is interrupted, blood glucose falls, and further stabilisation at these lower levels is dependent on the activa-

Table 3 Insulin dosage and glucose-6-phosphatase activity

Insulin (units/kg/h postnatal life $\times 10^3$)	V_{max} (nmol/min/mg)	<i>p</i> Value
0 (n=22)	76 (12)	
<10 (n=6)	134 (38)	0.06
10-15 (n=4)	145 (25)	0.03
15+ (n=4)	222 (46)	0.0002

Results are mean (SE).

p Values, for comparison of result with that for infants receiving no insulin treatment, were calculated with Student's *t* test using the Instat program for Macintosh computers.

tion of glycogenolysis and gluconeogenesis in response to regulation by postnatal changes in glucagon, catecholamines, and cortisol.²⁵⁻²⁶ Blood glucose concentrations gradually increase over the next few days with continued maturation of gluconeogenesis and increases in enteral intake.²⁷⁻²⁸ Preterm infants have lower hepatic glycogen reserves,²⁴ lower activities of key gluconeogenic enzymes,¹⁴⁻¹⁵ an initially limited hormonal response,²⁹ and, where regimens of postnatal care were similar to those of term infants, blood glucose values were not only lower but the postnatal rise was slower.³⁰ Hypoglycaemia is associated with cerebral damage in infants,¹⁻²⁻³¹ and in situations in which hepatic glucose-6-phosphatase activity is low—for example, in type I glycogen storage disease⁶—episodes of low blood glucose are common. Hepatic glucose-6-phosphatase activity is also low in preterm infants,¹⁴⁻¹⁵⁻¹⁸ and episodes of hypoglycaemia are common.²⁻³⁻¹⁶ The most likely explanation for most episodes of low hepatic glucose-6-phosphatase activity in preterm infants is delayed or abnormal postnatal development of enzyme expression.

Regulation of metabolism in low birthweight infants has consequences for not only the perinatal period but for long term regulation of glucose homeostasis. Failure during early development to correctly set the basal levels of critical enzymes in a variety of tissues—for example, liver and pancreatic islets—may lead to the evolution of overt disease in adulthood—for example, type II diabetes mellitus. Low levels of expression of glucokinase, which catalyses the reverse reaction to that catalysed by glucose-6-phosphatase, have been shown to cause MODY (a form of early onset type II diabetes mellitus³²). Several patients with low levels of glucose-6-phosphatase system activity (with type Ic glycogen storage disease) have also developed type II diabetes mellitus.³³⁻³⁴ It seems possible that genetic or developmental causes of low levels of enzyme expression will result in the same long term phenotype. It is therefore important to determine the factors regulating glucose-6-phosphatase activity in low birthweight infants, so that treatment strategies can be devised in early development to prevent the long term consequences of adult onset disease and also cerebral handicap resulting from hypoglycaemic episodes in early infancy.

The association of dopamine administration and lower hepatic glucose-6-phosphatase activity in preterm infants was just at the limit of significance ($p = 0.05$). Only seven infants were given dopamine; of these, four did not receive insulin and only two had respiratory

Table 2 Glucose-6-phosphatase activity in human liver microsomes

Source of hepatic microsomal samples	V_{max} (nmol/min/mg)	K_m (mM)
All preterm infant study group (n=36)	109(13)*	0.97 (0.11)
Control term infants (n=20)	340(40)	0.80 (0.10)
Study group without therapeutic insulin (n=22)	76(12)	0.97 (0.13)
Study group with therapeutic insulin (n=14)	162 (23)†	0.97 (0.21)
Study group without RDS (n=7)	50 (16)	0.90 (0.27)
Study group with RDS (n=29)	124 (15)‡	0.99 (0.12)
Study group without dopamine (n=29)	122 (15)	1.09 (0.13)
Study group with dopamine (n=7)	57 (16)	0.60 (0.12)

Results are mean (SE).

* $p < 0.0001$ compared with control term infants; † $p < 0.0008$ compared with study group without insulin treatment; ‡ $p < 0.05$ compared with study group without RDS (respiratory distress syndrome). *p* values were calculated with Student's *t* test using the Instat program for Macintosh computers.

distress syndrome. Dopamine has not been reported to change glucose-6-phosphatase expression, and any effects of dopamine administration on glucose-6-phosphatase activity are therefore likely to be secondary to its well established effects on circulating hormone levels—for example, insulin and glucagon.³⁵

In a different cohort of 109 preterm infants from the same neonatal intensive care unit, at the same time period, who survived the first five days of life, episodes of high blood glucose were found about three times more often in infants with severe respiratory distress syndrome (fractional inspired oxygen (F_{iO_2}) > 0.51).¹⁶ In this study, infants with respiratory distress syndrome (mean (SE) F_{iO_2} 0.81 (0.04)) had higher levels of glucose-6-phosphatase activity than those without respiratory distress syndrome. Severe respiratory distress syndrome is associated with higher circulating levels of counter-regulatory hormones such as catecholamines and glucocorticoids. Both dexamethasone and cyclic AMP have been shown to increase levels of transcription of the human glucose-6-phosphatase gene,³⁶ and it seems likely that the increased expression of glucose-6-phosphatase activity and protein in infants with respiratory distress syndrome is related to the increased levels of circulating counter-regulatory hormones.

The factor that correlated most closely with V_{max} of glucose-6-phosphatase activity was total insulin prescribed per kg body weight over the postnatal life of the infant. The levels of hepatic glucose-6-phosphatase activity in these preterm infants correlate well with levels of glucose-6-phosphatase protein expression. We have previously shown that, in neonatal term infants, glucose-6-phosphatase activity also correlates with glucose-6-phosphatase protein expression.¹⁴ Insulin was used as part of the treatment of hyperkalaemia and for the control of significant hyperglycaemia, and these antecedent conditions may have altered a hormone or metabolite that regulated the glucose-6-phosphatase gene. Renal thresholds for glucose are lower in preterm infants, and significant hyperglycaemia, which is relatively common in extremely sick neonates^{16 37} and results in osmotic diuresis and dehydration, occurred in two infants in this study who were treated with insulin.

It has been well known since the 1950s¹⁰ that acute administration of insulin to animals produces a decrease in glucose-6-phosphatase activity, and more recently insulin has been shown to decrease transcription of the human glucose-6-phosphatase gene.¹² The association that we found between repeated insulin administration (units/kg/h postnatal life $\times 10^3$) and increased liver glucose-6-phosphatase expression was therefore surprising. The association did not appear to be a short term effect of insulin on glucose-6-phosphatase activity as there was no significant difference in glucose-6-phosphatase activity when the interval between the last administration of insulin was less than five hours and when it was given more than 20 hours previously. The administration of insulin/glucose (n = 12) or insulin alone

(n = 2) to the cohort of preterm infants appeared to have the same effect, although it is not possible to perform meaningful statistical analysis as one group only contained two infants. As part of routine care, all infants had intravenous infusions of glucose at standard rates per kg body weight and days of postnatal age, and it is therefore unlikely that additional boluses of glucose at the time of insulin administration were the primary cause of the increased glucose-6-phosphatase activity. Preterm infants during the first five days of life are likely to have very different basal levels of a variety of hormones from those of either well term infants or adults, and these are likely to be influenced by both gestational age and severity of illness, as has been well documented for thyroid hormones (for a review see Burrow *et al*³⁸). It is well known that preterm infants have immature and often exaggerated counter-regulatory responses to hormones. It is therefore not possible to predict with certainty the counter-regulatory responses in low birth-weight infants to repeat insulin administration based on either previous studies on adults or a variety of animal species. However, it seems likely that repeated insulin administration may cause considerable changes in levels of other hormones—for example, catecholamines and glucocorticoids, which are known to upregulate glucose-6-phosphatase activity in liver. Alternatively, insulin decreases blood glucose levels (presumably by increasing peripheral uptake of glucose) as well as changing the blood levels of other metabolic intermediates—for example, ketone bodies and amino acids. Therefore alterations in the regulation of hepatic glucose-6-phosphatase expression could also be occurring in response to changes in metabolite levels—for example, in very recent experiments *in vitro* we have shown that the transcription of the glucose-6-phosphatase gene can be regulated by glucose¹³ and the transcription of many other key liver genes have been shown to be regulated by dietary factors³⁹.

All previous work on the elevation of hepatic glucose-6-phosphatase in diabetic states,^{8 9} the decrease in hepatic glucose-6-phosphatase activity in response to insulin administration,^{10 11} as well as the decreased transcription of the human glucose-6-phosphatase gene in response to insulin¹² suggest that administration of insulin to preterm infants is associated with decreased glucose-6-phosphatase expression. However, the opposite response occurs. This completely unpredicted response of elevated hepatic glucose-6-phosphatase levels in preterm infants to whom boluses of insulin had been administered means that it is important to carry out prospective studies on preterm infants to establish (a) their normal basal levels of hormones and metabolic intermediates and (b) their counter-regulatory responses to hormone administration. This information is essential because current clinical practice in the management of preterm infants involves the administration of a variety of hormones—for example, dexamethasone, insulin, and glucagon—and it is widely assumed that these will invoke the same responses as previously

shown in healthy adults or animal models. Clearly this current study indicates that this is not always the case. The current lack of knowledge of the responses of preterm babies to hormonal treatment also raises the possibility that hormonal administration, especially at key times in development like the neonatal period, could adversely set key glucostatic mechanisms in the low birthweight infants, which may have adverse long term consequences and in extreme cases could lead directly to adult onset of disease such as diabetes mellitus.

This work was supported by grants from the Scottish Home and Health Department (to A B and R H), British Diabetic Association (to A B), Wellcome Trust (to R H), Tenovus (Scotland) (to R H and A B), Paediatric Metabolic Research Trust (to R H), Babes in Arms (to A B), Scottish Cot Death Trust (to A B and R H), Research Trust for Metabolic Diseases in Children (to A B), and the Northwood Charitable Trust (to A B). A B was a Lister Institute Research Fellow. We thank Mrs Pamela Houston for excellent technical assistance and Dr Simon Ogston for advice on statistical analysis.

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Arch Dis Child Fetal Neonatal Ed 2000 82: F228-F232
doi: 10.1136/fn.82.3.F228

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